A Working Document

NIH Research And Other Efforts Related To The Menopausal Transition

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The Office of Research on Women's Health

and the

Coordinating Committee on Research on Women's Health

National Institutes of Health

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TABLE OF CONTENTS

Introduction

The median age of women at cessation of menstrual bleeding is 50 to 51 years. With an average life expectancy of 79.7 years, most women can expect to spend one-third to one-half of their lives post-menopause. In the United States alone, there are an estimated 41.75 million women over age 50, and in 2000, 1.802 million women (4,200 per day) reached menopause[a]. In addition, according to a 1998 study, one in three women between ages 45 and 64 were on hormone replacement therapy[b] (HRT), and there were about 17.5 million women total taking HRT to combat the biological effects of menopause[c]. Understanding the biology, symptomology, and socio-cultural implications of the menopausal transition is essential in addressing the health concerns of the aging female population. Therefore, the Office of Research on Women's Health (ORWH) is collaborating with NIH Institutes and Centers (IC) to develop a comprehensive report on NIH supported research and programs on the menopausal transition.

Initial information for this report was obtained through queries of the NIH Computer Retrieval of Information on Scientific Projects database (CRISP) and the National Library of Medicine website, www.ClinicalTrials.gov. Results of these queries were forwarded to the appropriate IC for verification, or revision. This report summarizes the basic science and clinical research, recent research results, and pending research studies on the menopausal transition currently funded by each Institute and Center, as provided through the Coordinating Committee on Research on Women's Health (CCRWH) representative from each NIH component.

Beginning with the definition of menopause as stated in the "World Health Report 1998," published by the World Health Organization (WHO), this report provides a summary, by IC, of menopause related research currently being funded by the NIH. Three IC's reported no current research on menopause: the National Institute of General Medical Sciences (NIGMS), the National Human Genome Research Institute (NHGRI), and the National Institute on Deafness and Other Communication Disorders (NIDCD).

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[a] North American Menopause Society, www.menopause.org/aboutm/stats.html
[b] "Health Concerns Across A Woman's Lifespan: The Commonwealth Fund 1998 Survey Of Women's Health." Collins, K.S., Schoen, C., Joseph, S., Duchon, L., Simantov, E., Yellowitz, M. May 1999.
[c] "Study: Hormones Don't Protect Women From Heart Disease." Okie, S.Washington Post. July 24, 2001.

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From the World Health Report, 1998
World Health Organization, Geneva, Switzerland

TERM	SOURCE
Menopause (natural menopause) The term natural menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhoea, for which there is no other obvious pathological or physiological cause. Menopause occurs with the final menstrual period (FMP), which is known with certainty only in retrospect a year or more after the event. An adequate biological marker for the event does not exist.	WHO*
Perimenopause The term perimenopause should include the period immediately prior to the menopause (when the endocrinological, biological, and clinical features of approaching menopause commence) and the first year after menopause.	WHO
Menopausal transition The term menopausal transition should be reserved for that period of time before the FMP when variability in the menstrual cycle is usually increased.	WHO
Climacteric This phase in the aging of women marks the transition from the reproductive phase to the non-reproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.	IMS**
Climacteric syndrome The climacteric is sometimes, but not necessarily always, associated with symptomatology. When this occurs, it may be termed the "climacteric syndrome."	IMS
Premenopause The term premenopause is often used ambiguously to refer to the one or two years immediately before the menopause or to refer to the whole of the reproductive period prior to the menopause. The group recommended that the term be used consistently in the latter sense to encompass the entire reproductive period up to the FMP.	WHO
Postmenopause The term postmenopause is defined as dating from the FMP, regardless of whether the menopause was induced or spontaneous.	WHO
Premature menopause Ideally, premature menopause should be defined as menopause that occurs at an age more than two standard deviations below the mean estimated for the reference population. In practice, in the absence of reliable estimates of the distribution of age	WHO

at natural menopause in populations in developing countries, the age of 40 years is frequently used as an arbitrary cut-off point, below which menopause is said to be premature.

Induced menopause WHO

The term, induced menopause, is defined as the cessation of menstruation, which follows either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (e.g. by radiation or chemotherapy).

**WHO – World Health Organization*
***IMS – International Menopause Society*

MENOPAUSE RELATED RESEARCH
By Institute or Center

NATIONAL CENTER FOR RESEARCH RESOURCES

(NCRR)

National Center for Research Resources

The National Center for Research Resources (NCRR) develops and supports critical research technologies which underpin health-related research to maintain and improve the health of our Nation's citizens. NCRR supports shared resources, sophisticated instrumentation and technology, animal models for study of human disease, clinical research, and research capacity building for underrepresented groups.

Through its support of multidisciplinary research, NCRR is uniquely positioned to provide either primary research support or provide resource support in partnership with other Institutes or Centers to address emerging clinical and basic research needs, such as the study of menopause. Expansion of NCRR's present efforts in new biotechnologies and instrumentation, development of animal models, and clinical research will foster interdisciplinary collaborations and advance NIH's efforts to study menopause.

Age-related Osteoporosis

An estimated 10 million Americans, 80 percent of them women, have osteoporosis, a dangerous thinning of the bones. Another 28 million suffer from low bone mass, an early warning sign of the disease, which can lead to painful, debilitating breaks. Osteoporosis is associated with a fall in estrogen after menopause. Replacing estrogen with supplements can slow the erosion of bone, as can a number of drugs. In a recent study at the University of Connecticut, NCRR-supported investigators Prestwood and colleagues compared three daily doses of the estrogen estradiol – 0.25 mg, 0.5 mg and 1 mg, the latter being the typical treatment dose taken by post-menopausal women -- and placebo in women age 65 and over. To gauge how well the treatments worked, the scientists looked for markers related to bone turnover at regular intervals over the three-month study. All doses of estrogen helped control bone destruction, but the 0.25 mg dose yielded essentially the same response as the 1.0 mg dose. But the women taking the 0.25 mg dose of estrogen reported less breast tenderness, and only one woman in the 0.25 mg group had bleeding or spotting, compared with eleven in the 0.5 and 1 mg groups. And while women taking 1 mg had a marked increase in the thickness of the womb tissue, those in the 0.25 mg and placebo groups did not. In summary, it appears that a pared-down of estrogen may do a woman's bones as much good as the usual, higher dose, but with fewer side effects and potentially less risk of uterine and breast tumors.

To avoid post-menopausal loss of calcium leading to osteoporosis, many women are prescribed estrogen pills to make up for their own lack of production of this hormone at that time. Unfortunately, in addition to its beneficial affect on bones, estrogen also affects the uterus and breasts of women, thus increasing the risk of cancer in these sites. A new medication, raloxifene hydrochloride, is a so-called selective estrogen modulator, characterized by its ability to increase bone mineral density (BMD) and decrease biochemical markers of bone turnover in postmenopausal women without stimulatory effects on the breast and uterus. However, the nature of these changes and the efficacy of raloxifene compared to estrogen treatment are not known. In this study, NCRR-supported investigators Prestwood et al the University of Connecticut followed two groups of post-menopausal subjects for bone architecture, bone turnover, and BMD: one group on estrogen replacement and the other on raloxifene for up to 24 weeks. Bone mineralization did not change in either group. Most markers of bone resorption and formation decreased in both groups but to a greater degree in the group on estrogen. Total body and lumbar spine BMD increased from baseline in both groups, with a greater increase in the group on estrogen. Thus, raloxifene is an alternative to estrogen for the

prevention and treatment of osteoporosis in postmenopausal women, an important finding for those who cannot or chose not to take estrogen.

Because of the prevalence of osteoporosis among post-menopausal women, hip fracture is a major health problem for this population. Its incidence varies among the populations of different countries and is directly related to animal protein intake, a finding that suggests that bone integrity may be compromised by endogenous acid production consequent to the metabolism of animal proteins. If that is so, vegetable foods might provide a countervailing effect, because they are a rich source of base (bicarbonate) in the form of metabolizable organic anions, which can neutralize protein-derived acid and supply substrate (carbonate) for bone formation. In this study, supported by NCRR-supported investigators Frassetto, Morris and Sebastian at the University of California, San Francisco, analyzed reported hip fracture incidence (HFI) data from 33 different countries, in women aged 50 years and older, in relation to corresponding country-specific data on per capita consumption of vegetable and animal foods as reported by the United Nations Food and Agriculture Organization. The results were that HFI varied directly with total and animal protein intake and inversely with vegetable protein intake. The countries in the lowest tertile of HFI (n = 11) had the lowest animal protein consumption, and invariably, vegetable protein (VP) consumption exceeded the country's corresponding intake of animal protein (AP): VP/AP > 1.0. By contrast, among the countries in the highest tertile of HFI, animal protein intake exceeded vegetable protein intake in nearly every case (10 of 11 countries). Among all countries, HFI correlated inversely and exponentially with the ratio of vegetable/animal protein intake and accounted for 70% of the total variation in HFI. Adjusted for total protein intake, vegetable food consumption was an independent negative predictor of HFI. All findings were similar for the subset of 23 countries whose populations are predominantly Caucasian. The authors conclude that the findings suggest that the critical determinant of hip fracture risk in relation to the acid-base effects of diet is the net load of acid in the diet. Moderation of animal food consumption and an increased ratio of vegetable/animal food consumption may confer a protective effect.

Menopausal Heart Disease

Atherosclerosis is an accumulation of fatty material in the walls of arteries, causing narrowing of the vessels. Early in life, women have a relatively low incidence of coronary artery disease due to atherosclerosis. However, after menopause (with its accompanying loss of natural estrogen production), women are at high risk of this type of heart disease. Popular thinking concluded that estrogen was protective of the coronary arteries in women. It was, therefore, easy to imagine that estrogen replacement therapy in this population would reduce the risk of this type of heart disease. In this study, a group of post-menopausal women with verified coronary heart disease were followed by Herrington et al at the Wake Forest University Medical School under three different regimens: estrogen therapy alone; estrogen therapy plus progesterone; and placebo (sugar pill). Blood levels of various lipids known to be associated with heart disease, significantly improved after treatment with either estrogen alone or estrogen plus progesterone, but not in the placebo group. Despite the improvement in laboratory values, neither of the estrogen receiving groups showed less progression of the heart disease, suggesting that post-menopausal women with atherosclerotic heart disease do not derive cardiac benefit from estrogen replacement with or without progesterone.

NCRR References

1. Frassetto LA, Todd KM, Morris RC, Jr., Sebastian A. Worldwide incidence of hip fracture in elderly women: Relation to consumption of animal and vegetable foods. Journal of Gerontology: MEDICAL SCIENCES 2000; 55A:(10)M585-M592.

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6. Prestwood KM, Kenny AM, Unson C, Kulldorff M. The effect of low dose micronized 17b-estradiol on bone turnover, sex hormone levels, and side effects in older women: A randomized, double-blind, placebo-controlled study. J.Clin.Endocrinol.Metab. 2000; 85:(12)4462-4469.

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8. Sellmeyer DE, Stone KL, Sebastian A, Cummings SR, Study of Osteoporotic Fractures Research Group. A high ratio of dietary animal to vegetable protein increases the rate of bone loss and risk of fracture in postmenopausal women. Am.J.Clin.Nutr. 2000; 73:118-22.

9. Shah N, Evans WS, Bowers CY, Veldhuis JD. Oral estradiol administration modulates continuous intravenous growth hormone (GH)-releasing peptide-2-driven GH secretion in postmenopausal women. J.Clin.Endocrinol.Metab. 2000; 85:(8)2649-2659.

NCRR Menopause Related Grants

Grant Number	Title	Principal Investigator	Institution
P41RR00954-24	SHORT TERM MOD WGHT LOSS & RESIST TRAINING IN NON DIABETIC POST MENOPAUSAL WOMEN	JOSEPH, LYNDON JO	WASHINGTON UNIVERSITY
K23RR16067-01	WOMEN AT HIGH RISK FOR CAD AFTER MENOPAUSE: BENEFITS OF ERT	CARR, MOLLY C	UNIVERSITY OF WASHINGTON
M01RR00032-40	POST MENOPAUSAL HORMONE THERAPY & INTRA ABDOMINAL FAT	GOWER, BARBARA A	UNIVERSITY OF ALABAMA AT BIRMINGHAM
M01RR00042-40	ROLE OF HYPOTHALAMIC AGING IN MENOPAUSE	REAME, NANCY E	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01RR00042-40	ABOLISHING INCREASES IN INSULIN SENSITIVITY IN POSTMENOPAUSAL WOMEN	BORER, KATARINA T	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01RR00042-40	EFFECT OF RALOXIFENE ON INSULIN SENSITIVITY IN POSTMENOPAUSAL WOMEN	SUPIANO, MARK A	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01RR00042-40	EFFECTS OF TRAINING INTENSITY ON CHD RISK FACTORS IN POSTMENOPAUSAL WOMEN	BORER, KATARINA T	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01RR00046-40	LCCC 9725: PHARMACOKINETIC STUDY OF GENISTEIN IN POST MENOPAUSAL WOMEN	ZEISEL, STEVEN J	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL
M01RR00046-40	EFFECTS OF EXERCISE ON SERUM ESTROGENS IN POSTMENOPAUSAL WOMEN	MEYER, WILLIAM R	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL
M01RR00051-39	EXERCISE ON RISK FACTORS FOR CARDIOVAS DISEASE IN POSTMENOPAUSAL WOMEN	SEALS, DOUGLAS	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01RR00054-39	MENOPAUSAL SYMPTOMS STUDY	WOODS, MARGO	NEW ENGLAND MEDICAL CENTER HOSPITALS
M01RR00055-39	EFFECTS OF PROGESTERONE IN POSTMENOPAUSAL & NORMALLY CYCLING WOMEN	DE WIT, HARRIET	UNIVERSITY OF CHICAGO
M01RR00055-39	ESTROGEN IN POSTMENOPAUSAL WOMEN: DRUG PREFERENCE IN HUMANS STUDY 1A & 2A	DE WIT, HARRIET	UNIVERSITY OF CHICAGO

Grant Number	Title	Principal Investigator	Institution
M01RR00056-39	RANDOMIZED DBL BLIND HORMONE REPLACEMENT IN POSTMENOPAUSAL WOMEN W/ SLE	MANZI, SUSAN	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01RR00056-39	EFFECT OF PHYTOESTROGEN SUPPLEMENTATION ON POST MENOPAUSAL ENDOMETRIUM	BALK, JUDY	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01RR00065-38	DHEA ON BONE METABOLISM IN POSTMENOPAUSAL WOMEN	BISKOBING, DIANE	VIRGINIA COMMONWEALTH UNIVERSITY
M01RR00073-38	OVARIAN STEROIDS IN MENOPAUSAL WOMEN W/ ENDOMETRIAL CANCER	NAGAMANI, MANUBAI	UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
M01RR00079-37	SALT & POTASSIUM BICARBONATE DIETS & BONE METABOLISM IN POSTMENOPAUSAL WOMEN	SEBASTIAN, ANTHONY	UNIVERSITY OF CALIFORNIA SAN FRANCISCO
M01RR00080-38	CLINICAL TRIAL: EFFICACY OF FISH OIL AFTER MENOPAUSE	UTIAN, WULF H	CASE WESTERN RESERVE UNIVERSITY
M01RR00088-37	EFFECTS OF EXOGENOUS MELATONIN ON SLEEP IN POST MENOPAUSAL WOMEN W/ INSOMNIA	WURTMAN, JUDITH J	MASSACHUSETTS INSTITUTE OF TECHNOLOGY
M01RR00095-40	INTERINDIVIDUAL VARIABILITY IN ESTROGEN METABOLISM IN POSTMENOPAUSAL WOMEN	ROBIN, DEBORAH	VANDERBILT UNIVERSITY
M01RR00095-40	VARIABILITY IN ESTROGEN METABOLISM IN POSTMENOPAUSAL WOMEN	ROBIN, DEBORAH	VANDERBILT UNIVERSITY
M01RR00109-36	ENERGETIC ADAPTATION TO MENOPAUSE TRANSITION	TOTH, MICHAEL	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR00109-36	ESTROGEN MODULATION EFFECTS ON CHOLINERGIC FUNCTION IN POST MENOPAUSAL WOMEN	NEWHOUSE, PAUL A	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR00109-36	EFFECT OF HRT ON CARDIOVASCULAR HEMODYNAMICS & BLOOD VOLUME IN MENOPAUSAL WOMEN	SITES,, CYNTHIA K	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR00109-36	MECHANISM OF MUSCLE PROTEIN LOSS IN MENOPAUSE	MATTHEWS DWIGHT E	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR00125-37	EFFECTS OF ACUTE TRYPTOPHAN DEPLETION IN POSTMENOPAUSAL WOMEN	EPPERSON, NEILL	YALE UNIVERSITY

Grant Number	Title	Principal Investigator	Institution
M01RR00585-29	IF & HOW ESTROGEN REPLACEMENT THERAPY REGULATES PTH IN POSTMENOPAUSAL WOMEN	RIGGS, B LAWRENCE	MAYO CLINIC ROCHESTER
M01RR00633-28	PREVENTION OF BONE LOSS IN EARLY POSTMENOPAUSAL WOMEN W/ CALCIUM	PAK, CHARLES YC	UNIVERSITY OF TEXAS SW MED CTR/DALLAS
M01RR00633-28	SIMVASTIN/HRT IN POSTMENOPAUSAL WOMEN W/ NIDDM	GARG, ABHIMANYU	UNIVERSITY OF TEXAS SW MED CTR/DALLAS
M01RR00633-28	NEOSTEN & ALENDRONATE IN MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS	RUBIN, CRAIG D	UNIVERSITY OF TEXAS SW MED CTR/DALLAS
M01RR00645-29	MENOPAUSAL HOT FLASHES: EFFECT OF CHINESE HERBAL PREPARATION	KRONENBERG, FREDI	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01RR00645-29	FIBRINOLYTIC POTENTIAL OF ESTROGEN IN PRE PERI & POST MENOPAUSAL WOMEN	GIARDINA, ELSA-GRACE	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01RR00645-29	HORMONE REPLACEMENT THERAPY IN POST MENOPAUSAL WOMAN W/ TYPE 2 DIABETES	TUCK, CATHERINE	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01RR00847-27	INFLUENCE OF POSTMENOPAUSAL ESTROGEN REPLACEMENT ON GH SECRETION	VELDHUIS, JOHANNES D	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
M01RR00847-27	INFLUENCE OF POSTMENOPAUSAL ESTROGEN REPLACEMENT ON GROWTH HORMONE SECRETION	VELDHUIS, JOHANNES D	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
M01RR00847-27	INFLUENCE OF POSTMENOPAUSAL ESTROGEN REPLACEMENT ON GH AUTO NEGATIVE FEEDBACK	VELDHUIS, JOHANNES D	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
M01RR00865-27	DIET & ESTROGEN METABOLISM IN POSTMENOPAUSAL WOMEN	HEBER, DAVID	UNIVERSITY OF CALIFORNIA LOS ANGELES
M01RR00865-27	ESTROGEN REPLACEMENT THERAPY VS PLACEBO IN POSTMENOPAUSAL WOMEN	RAPKIN, ANDREA	UNIVERSITY OF CALIFORNIA LOS ANGELES
M01RR01066-23	MENOPAUSE TRANSITION IN BLACK & WHITE WOMEN: ASSESS OF RACIAL DIF IN BONE DENS	FINKELSTEIN, JOEL S	MASSACHUSETTS GENERAL HOSPITAL
M01RR01066-23	PREVENTION OF EARLY POSTMENOPAUSAL BONE LOSS W/ PARATHYROID HORMONE	FINKELSTEIN, JOEL S	MASSACHUSETTS GENERAL HOSPITAL

Grant Number	Title	Principal Investigator	Institution
M01RR02635-16	ALCOHOL EFFECTS ON NEUROENDOCRINE FUNCTION IN POSTMENOPAUSAL WOMEN	GINSBURG, ELIZABETH	BRIGHAM AND WOMENS HOSPITAL
M01RR02635-16	ADDITION OF TESTOSTERONE TO HRT ENHANCES QOL & LIBIDO IN POSTMENOPAUSAL WOMEN	GINSBURG, ELIZABETH	BRIGHAM AND WOMEN'S HOSPITAL
M01RR02635-16	PHASE II TRIAL OF CP336156 FOR PREV OF BONE LOSS IN POSTMENOPAUSAL WOMEN	LEBOFF, MERYL S	BRIGHAM AND WOMENS HOSPITAL
M01RR02635-16	ESTROGEN & RECEPTOR MODULATOR ON THYROID FUNCT IN MENOPAUSAL & HYPOTHYROID WOMEN	BRAVERMAN, LEWIS	BRIGHAM AND WOMENS HOSPITAL
M01RR02719-15	SODIUM SENSITIVITY IN POSTMENOPAUSAL WOMEN	ANDERSON, DAVID E	JOHNS HOPKINS UNIVERSITY
M01RR06192-07	EFFECT OF IDOXIFENE ON BONE HISTOMORPHOMETRY IN POSTMENOPAUSAL WOMEN	PRESTWOOD, KAREN	UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
M01RR06192-07	EFFECT OF HORMONE REPLACEMENT THERAPY ON BONE IN OLDER WOMEN	PRESTWOOD, KAREN	UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
M01RR06192-07	EFFECT OF ENBREL ON BONE TURNOVER IN POSTMENOPAUSAL WOMEN	PRESTWOOD, KAREN	UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
M01RR07122-09	DIETARY SOY SUPPLEMENT IN MENOPAUSAL WOMEN (SEA)	BURKE, GREGORY L	WAKE FOREST UNIVERSITY
M01RR07122-09	POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY AFTER CORONARY BYPASS SURGERY (EAGER)	HERRINGTON, DAVID M	WAKE FOREST UNIVERSITY
M01RR10710-03	INDUCING BONE FORMATION BY LOW DOSE DOXYCYCLINE FOR POSTMENOPAUSAL OSTEOPOROSIS	GRUBER, BARRY	STATE UNIVERSITY NEW YORK STONY BROOK
M01RR10732-06	CARDIOVASCULAR RISK FACTORS & DIET TRACKING IN POSTMENOPAUSAL WOMEN W/ CAFFEINE	LLOYD, THOMAS A	PENNSYLVANIA STATE UNIV HERSHEY MED CTR
P51RR00163-41	MENOPAUSE IN RHESUS MACAQUE NEUROENDOCRINE PERSPECTIVE	URBANSKI, HENRYK F	OREGON HEALTH SCIENCES UNIVERSITY
P51RR00169-39	MENOPAUSAL TRANSITION USING AGED MACAQUES	SHIDELER, SUSAN E	UNIVERSITY OF CALIFORNIA DAVIS

NATIONAL CANCER INSTITUTE

(NCI)

National Cancer Institute

Description: This document is a collection of links to websites that contain cancer-related information from the NCI on menopause and hormone replacement therapy. Provided below are the titles of the websites, the html addresses to those sites, and brief summaries of the information provided in those sites. Included also, is information about clinical trials that are currently being funded by NCI.

In addition to this document, a spreadsheet is provided containing research grants, which have been funded recently or are currently being funded by NCI. The grant number, research area, and abstract are included in this spreadsheet.

Search Words: *menopause; hormone replacement therapy (HRT); estrogen replacement therapy (ERT)*

Fact Sheets and Question and Answer on Menopause and Hormone Replacement Therapy

1. Questions and Answers about Hormone Replacement Therapy
   http://newscenter.cancer.gov/pressreleases/hormone_qa.html

   Summary: A fact sheet produced by NCI's Office of Cancer Communications which answers commonly asked questions about Hormone Replacement Therapy (HRT). Included in the questions answered are: what is HRT; what is menopause; and what are the health implications of HRT. This article also includes an extensive list of references concerning HRT and menopause.

2. Fact Sheet on Menopause and HRT
   http://cis.nci.nih.gov/fact/3_10.htm

3. Breast Cancer Treatment for Health Professionals: Hormone replacement therapy
   http://www.nci.nih.gov/cancer_information/doc_pdq.aspx?version=provider&viewid=53d97cba-89a2-45d4-b55d-b7b5ad7dc2dd#5

   Summary: A brief description of the dilemmas and benefits of using hormone replacement therapy, geared to physicians looking for information on breast cancer treatment.

4. Breast Cancer Treatment for Patients: Hormonal Therapy
   http://www.nci.nih.gov/cancer_information/doc_pdq.aspx?version=patient&viewid=53d97cba-89a2-45d4-b55d-b7b5ad7dc2dd#k20

   Summary: This is a summary geared to patients, explaining the benefits and side effects of using hormonal therapy for the treatment of breast cancer.

5. Cancer Facts: Menopausal Hormone Replacement Therapy (HRT)
   http://cis.nci.nih.gov/fact/3_10.htm; http://cis.nci.nih.gov/fact/pdfdraft/3_risk/fs3_10.pdf

Summary: This is a fact sheet, which describes menopause, the symptoms of menopause, HRT, benefits and concerns of HRT, and possible alternatives to HRT for treatment of menopausal symptoms. This site also includes a list of resources and contact information concerning this topic.

Breast Cancer and Adjuvant Hormonal Therapies

6. Adjuvant Therapy for Breast Cancer
http://www.nlm.nih.gov/pubs/cbm/adjuvant_therapy_breast_cancer.html

Summary: This a literature review that discusses adjuvant breast cancer therapy which uses hormone therapy in conjunction with chemotherapy in order to slow the growth of breast cancer

7. NIH Consensus Panel Recommends a Range of Adjuvant Therapies for Women with Breast Cancer
http://consensus.nih.gov/cons/114/114_intro.htm;
http://www.nci.nih.gov/clinical_trials/doc.aspx?viewid=17831219-FAB1-4F19-9B7F-D5B3C9C02760

Summary: A NIH panel recommended hormonal therapy for women whose breast tumors contain estrogen receptors, regardless of age, menopausal status, tumor size, or whether the cancer had spread to nearby lymph nodes. The panel recommended chemotherapy with a combination of drugs for most pre- and post-menopausal women regardless of lymph node involvement or estrogen receptor status.

8. Tamoxifen Found to be Equally Effective For Black and White Women
http://newscenter.cancer.gov/pressreleases/tamoxifen_equal.html

Summary: A new analysis shows that Tamoxifen is as effective for black women as it is for white women in reducing the occurrence of "contralateral" breast cancer -- cancer that develops in the healthy breast after cancer in the opposite breast has been treated. In addition, the drug does not cause more side effects in black women, as some had originally feared.

9. More Data Show: 5 Years of Tamoxifen is Enough
http://www.nci.nih.gov/clinical_trials/doc.aspx?viewid=EB1AF9F5-088E-4E71-BD1E-4136E4117AD6

Summary: This document reports that women recovering from breast cancer that has not spread to the lymph nodes appear to gain no additional advantage by taking tamoxifen beyond the five years already shown to be most effective in preventing a relapse. More research needs to be done to determine if there are any benefits to continuing Tamoxifen beyond 5 years.

Breast Cancer and Menopause/Hormone Replacement Therapy

10. Study Shows Greater Risk of Breast Cancer with Estrogen-Progestin Therapy Compared to Estrogen Alone.
http://newscenter.cancer.gov/pressreleases/hrt.html

Summary: Researchers in this study found that combined estrogen-progestin replacement therapy is associated with a greater risk of breast cancer than estrogen alone. Both groups had a higher risk than non-users. Also included in this article are some findings concerning the effects of these hormones on

lean versus heavier women. Future studies on the long-term effects of progestin use are suggested.

11. Breast Density, Hormone Replacement, and Breast Cancer Risk
http://newscenter.cancer.gov/pressreleases/breastdensity.htm

Summary: Describes findings demonstrating that women taking postmenopausal estrogen/progestin have an increase in breast density on their mammograms, which may be linked to a higher incidence of breast cancer.

12. Premature Menopause in Survivors of Childhood Cancer
http://cancercontrol.cancer.gov/ocs/abstracts/sklar.html

Summary: This ongoing study sponsored by NCI's Office of Cancer Survivorship addresses the prevalence of early menopause, risk factors for early menopause, and early menopause's impact on quality of life in childhood cancer survivors.

Breast Cancer Prevention and Hormone Therapy

13. Cancer Facts: Breast Cancer Prevention Studies
http://cis.nci.nih.gov/fact/pdfdraft/4_preven/fs4_18.pdf

Summary: This article discusses several breast cancer prevention studies including studies dealing with the Study of Tamoxifen and Raloxifene (STAR) and Selective Estrogen Receptor Modulators (SERMs).

14. Cancer Facts: Questions and Answers About the Study of Tamoxifen and Raloxifene (STAR)
http://cis.nci.nih.gov/fact/4_19.htm

Summary: This Q & A fact sheet discusses Tamoxifen and Raloxifene as part of clinical prevention trials for menopausal women who are at a high risk for breast cancer.

15. Weighing the Risks and Benefits of Tamoxifen to Reduce Risk of Breast Cancer
http://newscenter.cancer.gov/pressreleases/tamoxifen.html

Summary: Investigators from the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) and their co-authors conclude that Tamoxifen is most beneficial for younger women with an elevated risk of breast cancer, but emphasize that a decision to take the drug depends on many factors, not just breast cancer risk.

16. Press Release: STAR Enrolls 6,139 Women in First Year; 16,000 More Women at Increased Risk of Breast Cancer Sought (8/00)
http://newscenter.cancer.gov/pressreleases/year1.html

Summary: This press release gives an update of the first year of the STAR (Study of Tamoxifen and Raloxifene) trial and includes information about how to enroll.

17. National Cancer Institute Launches Capital Area SERM Study
http://www.cancer.gov/clinical_trials/doc.aspx?viewid=B7982532-03F3-4316-9F94-9A2BDEB4F27C

Summary: This article briefly explains SERMs (Selective Estrogen Receptor Modulators), their possible benefits in reducing breast cancer, and offers information for women who are at high risk for breast cancer to participate in a SERM study.

Endometrial Cancer Prevention/Treatment and Hormone Replacement Therapy

18. CancerLit Topic Search: Endometrial Cancer and Hormone Replacement Therapy
http://www.nci.nih.gov/search/cancer_literature/results_cancerlit.aspx

    Summary: This site presents article abstracts from NCI's CancerLit database, which describe results from studies focusing on estrogen replacement therapy and endometrial cancer.

19. Cancer Facts: Questions and Answers About the Study of Estrogen Replacement Therapy in Women Treated for Uterine Cancer
http://cis.nci.nih.gov/fact/6_27.htm

    Summary: This is a Q & A sheet that answers questions about endometrial cancer, estrogen replacement therapy (ERT), and how ERT is related to endometrial cancer. A clinical trial on this area is described and links are included to further information on enrollment.

20. Clinical Trials: Endometrial Cancer and Hormone Replacement Therapy
http://www.nci.nih.gov/search/clinical_trials/results_clinicaltrials.aspx

    Summary: Estrogen replacement therapy may improve quality-of-life in postmenopausal women with endometrial cancer. It is not yet known whether estrogen replacement therapy will affect cancer recurrence. Three clinical trials are currently active focusing on these issues.

Alternatives to Hormone Replacement Therapy

21. A New Treatment for Hot Flashes: Antidepressants
http://www.cancer.gov/clinical_trials/doc.aspx?viewid=7C8200D5-C482-4D8D-B7C7-17242C5EEE46

    Summary: Women with breast cancer who suffer hot flashes as a symptom of menopause or effects of treatment now have an alternative to hormone replacement therapy; widely used antidepressant drugs. Results from a large study presented at the 2000 annual meeting of the American Society of Clinical Oncology showed that Venlafaxine (Effexor) substantially reduced hot flashes in 62 percent of women. Preliminary studies of three other antidepressants indicate similar promising results.

NCI Menopause Related Grants (8-2001)

(For active NCI grants on HRT go to: http://researchportfolio.cancer.gov/cgi-bin/search.pl?Search=hormone+replacement+therapy; For active NCI grants related to menopause go to: http://researchportfolio.cancer.gov/cgi-bin/search.pl?Search=menopause)

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA17054	2001	University of Southern California	Iatrogenic Causes of Cancer	Bladder Cancer, Blood Cancer, Breast Cancer, Cervical Cancer, Gastrointestinal Tract, Genital System, Female, Kidney Cancer, Leukemia, Liver Cancer, Lung Cancer, Nervous System, Respiratory System, Urinary System	Etiology/Exogenous Factors in the origin and cause of cancer	This proposal requests continued support for a Program Project Grant (PPG) to conduct epidemiologic and biostatistical research on iatrogenic causes of cancer by investigators at the Kenneth Norris Jr. (University of Southern California) Comprehensive Cancer Center. This PPG is currently in its 16th year of continuous funding. The professional staff of this Program consists of 11 epidemiologists and statisticians with major research interests in iatrogenic exposures and cancer. The Scientific Program of the current application consists of 3 case-control studies. The successful conduct of these 3 projects depends on 5 core resources. The 4 projects include the following: (1) A continuation of an ongoing case-control study of the relationship of hormone replacement therapy and breast cancer risk in postmenopausal women. An expanded study will allow more detailed and precise evaluation of duration and latency effects, the evaluation of interactions and adequate adjustment for confounding factors; (2) A continuation of an ongoing case- control study of analgesics and diuretics and renal cell carcinoma. Preliminary results suggest that acetaminophen is associated with a greater increment in risk than aspirin, but the strong correlation between different formulations requires larger sample sizes to determine independent effects; and A continuation of an ongoing case-control study of diagnostic radiation and acute myelogenous leukemia. Preliminary data suggest a dose response relationship between trunk x-rays and risk but results are not statistically significant. The major core resource for this PPG is the Cancer Surveillance Program, a rapid ascertainment population-based tumor registry. Other core resources include a Medical Record Retrieval Core for validating self-reported prescription medications, diagnostic and therapeutic radiation, a Control Identification Core for identifying neighborhood controls for case-control studies, a Statistical Core for developing strategies for analyzing the types of studies described above and an Administrative Core for overseeing the scientific direction of the PPG and handling its fiscal administration.
CA18119	2001	University of Illinois Urbana-Champaign	Antiestrogens--Mechanism of Antagonist Action	Breast Cancer	Biology/Cancer-Related Biology	Antiestrogens (AEs) are the most widely used agents for the treatment of hormone-responsive breast cancer, and the AE tamoxifen has also proven to be effective in preventing breast cancer. AEs are also unique ligands useful for understanding the tissue selective actions of certain estrogens, an important issue in menopausal hormone replacement therapy, and for probing the intriguing pharmacology of the two estrogen receptor (ER) subtypes, ERalpha and ERbeta, and their roles in breast cancer and other estrogen target cells. In this application, we are proposing to investigate two new aspects of the action of AEs. The first aspect deals with the ability of certain proteins (denoted PAAs for "Potentiators of Antiestrogen Activity") that we have identified recently, to enhance the potency of AEs as inhibitors of estrogens. The levels and activity of these small, estrogen receptor-selective proteins could account for the differential tissue selectivity of AEs and for the ability of ER-containing breast tumors to be either highly sensitive, or resistant to AE therapy. We propose to identify and characterize PAAs, by examining their roles as modulators of AE action in target cells and eterminants of hormonal resistance in breast cancer, by elucidating their interaction domains with ER, their subcellular distribution, and their interaction with other ER coregulators, and by performing structural analyses on PAA-ER complexes. The second aspect also derives from our recent work in which we have found that certain antioxidant/cytoprotective genes are upregulated by AEs and inhibited by estrogens. We propose to identify and analyze the regulation of genes selectively upregulated by AEs, by searching for other genes that are AE stimulated and estrogen suppressed, by analyzing the gene regulatory regions mediating the selective activation by AEs, by determining the ERalpha and ERbeta selectivity of this regulation, and by examining whether other antioxidant genes involved in cytoprotection against reactive oxygen species are upregulated by AEs. The studies we propose should provide significant new insight into how AEs act, what cellular factors determine their effectiveness and tissue selectivity, and how their gene regulating activities contribute to their beneficial antiproliferative, tumor suppressive, and cytoprotective actions in breast cancer treatment and prevention.

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA40356	2000	Brigham and Women's Hospital	A Prospective Study of Diet and Cancer in Women	Breast Cancer, Colon and Rectal Cancer, Endometrial Cancer, Gastrointestinal Tract, Genital System, Female, Lung Cancer, Melanoma, Not Site-Specific Cancer, Ovarian Cancer, Respiratory System	Etiology/Exogenous Factors in the origin and cause of cancer	We propose to continue our ongoing study of diet and cancer conducted in a cohort of 121,700 U.S. female registered nurses who have been followed with biennial questionnaires since 1976 and who are currently 47 to 72 years of age. Continued follow-up will permit assessment of lifestyle changes in this well characterized cohort of middle to older aged US women. Risk factors include, in addition to diet and post-menopausal hormones, physical activity, smoking, obesity (including waist to hip ratio), and reproductive factors. The dietary aspect of the study was begun in 1980 when the first semiquantitative food frequency questionnaire (SFFQ) was completed by approximately 89,000 women. An expanded version of the SFFQ was used in 1984, 1986 and 1990 and will be used in 1994 and 1998 to update diet. These data will provide exposure information both close in time to the diagnosis of cancer, which is likely to be important for a number of nutritional factors postulated to act in the later stages of carcinogenesis, and remote diet. With diet assessment repeated over 14 years of follow-up, we will examine change in diet in relation to cancer risk. Specific components of diet will be examined in relation to risk of breast, colon, lung, ovarian, and endometrial cancers, and melanoma. This proposed research will greatly strengthen our ability to test a wide variety of hypotheses relating dietary factors to the incidence of cancers. After 18 years of follow-up (assuming 90% power and an alpha error of 0.05) relative risks of 1.4, 1.4, 1.6, and l.16 for extreme quintiles of nutrient distributions can be detected for cancers of the breast, colon, lung, and melanoma respectively. A second major component of the study addresses relations between postmenopausal hormones and risk of cancer. Specific analyses will address type of hormone used. The analyses will assess the potential interaction between alcohol use and hormone replacement therapy on risk of breast cancer. In addition, risk benefit analyses will address life expectancy in relation to use of postmenopausal hormones and also moderate alcohol intake.
CA46475	2001	Brigham and Women's Hospital	Benign Breast Disease and Risk of Breast Cancer	Breast Cancer	Etiology/Exogenous Factors in the origin and cause of cancer	We propose to continue to evaluate subcategories of benign breast disease in relation to risk of breast cancer. In addition, interactions between these characteristics and established and hypothesized risk factors for breast cancer will be examined using prospectively collected data. In particular, we will examine interactions between atypical hyperplasia and family history of breast cancer, menopause, use of postmenopausal estrogens, past use of oral contraceptives and relative weight (weight/height2), alcohol intake, dietary fat, intake of vitamin A (preformed and carotene), vitamin E, and caffeine. The proposed study is nested case-control within the Nurses' Health Study, a cohort of 121,700 US female registered nurses, currently aged 444-69 who were enrolled in a prospective study of risk factors for breast cancer in 1976 and who have been followed with biennial questionnaires since then. In addition, we add 50 cases and their controls from the Nurses' Health Study II. An extensively validated semi-quantitative food frequency questionnaire administered in 1980 enables us to assess the dietary variables. We propose to obtain and review histopathology slides from an additional 500 women with breast cancer diagnosed between return of the 1988 NHS questionnaire and the 1996 questionnaire who have a history of an earlier biopsy for benign breast disease and 2218 controls randomly selected from among women with a history of biopsy for benign breast disease in the cohort. Slides will be independently reviewed in a blinded fashion by two pathologists and graded according to the classification system based on that of Dr.Page. An histopathologic aim is to define objective criteria for the architecture and morphology of atypical hyperplasia. The relative risk of breast cancer associated with subcategories of benign breast disease (nonproliferative, proliferative, atypical) will be calculated using the women with no history of benign breast disease in the Nurses' Health Study cohort as a reference group. Potential interactions with epidemiologic and dietary risk factors will be assessed by stratified and multivariate analysis. We will also analyze data from the Nurses' Health Study II to examine the relation between long term use of oral contraceptives before first pregnancy and risk of atypical hyperplasia on breast biopsy.
CA59736	2001	Fred Hutchinson Cancer Research Center	Factors Affecting Survival of Young Cancer Patients	Breast Cancer	Etiology/Interactions of Genes and/or Genetic Polymorphisms with Exogenous and /or Endogenous Factors	DESCRIPTION: This application for a competitive renewal of "Factors that affec survival of young breast cancer patients", seeks to extend for five more years the follow-up for recurrence and mortality of a population-based cohort of 128 women who were diagnosed with invasive breast cancer before age 45 during the years 1983 through 1992. These women provide the investigators with a unique opportunity to investigate the interrelationships between epidemiologic risk factor data, tumor characteristics, and breast cancer occurrence and/or mortality in a population-based setting where all cases of breast cancer in a defined geographic area could be assessed, eliminating potential biases impose by studies at referral centers or clinical trials, where women may self-select into the study and not be representative of women in general who get breast cancer. During the past five years, this cohort was followed through follow-up questionnaires and hospital chart reviews, and their tumor specimens were tested for characteristics related to aggressiveness and prognosis. It is important to extend follow-up of this cohort to a minimum of ten years since patient and tumor characteristics may have different relationships with short and long-term mortality. During the next five years, the investigators propose to (a) expand data collection and specimen analyses to the entire cohort (rather than the subgroup of 930 they originally proposed), (b) extend the minimum follow-up period for the entire cohort to ten years, (c) collect updated information on recurrences, treatment, the use of hormone eplacement therapy and childbearing after diagnosis, (d) add apoptotic index to the laboratory analyses, and(e) conduct comprehensive analyses of all of these data in relation to mortality and disease-free survival. Young women with many years of potential life to lose who do not fall into clear prognostic categories present a major challenge to clinicians. By gainin an understanding of the association between epidemiologic risk factors and tumor characteristics related to aggressiveness as well as actual risk of recurrence or death, it is possible to develop profiles of women at high risk for aggressive tumors who might benefit from aggressive treatment and of those with low risk tumors for whom such aggressive treatment may not be necessary.

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA60050	2001	Ohio State University	Premature Ovarian Failure in Breast Cancer Patients	Bone Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma, Breast Cancer	Cancer C ontrol, Survivorship and Outcomes Research/Patient Care and Survivorship Issues	Adjuvant chemotherapy reduces mortality rates in women with breast cancer. Because many breast cancer patients have prolonged survival after adjuvant treatment the long term health effects associated with adjuvant chemotherapy are important to evaluate. Premature ovarian failure (menopause) occurs in approximately 70% of premenopausal breast cancer patients who receive adjuvant chemotherapy. The resulting estrogen deficiency and premature menopause in women with breast cancer may result in accelerated loss of bone, and the risk for subsequent skeletal fractures (osteoporosis). To investigate whether breast cancer patients who develop chemotherapy-induced premature ovarian failure experience accelerated bone loss, in Specific Aim #1 we will prospectively examine bone mineral density and biochemical indices of skeletal homeostasis in premenopausal breast cancer patients who develop chemotherapy-induced premature ovarian failure. In Specific Aim #2 we will test whether nasal spray calcitonin, an inhibitor of bone resorption, prevents bone loss in these women. Premenopausal breast cancer patients with 0-3 axillary nodal metastases will be recruited to participate in this research study. One-hundred such women will undergo baseline evaluations of menstrual status, follicle-stimulating hormone (FSH), estradiol (E2), and progesterone, (P), reproductive history questionnaire, activity questionnaire, self-rating depression questionnaire, 3-day dietary evaluation, quantitative measurements of bone mineral density of the lumbar spine and proximal femur, and biochemical indices of skeletal homeostasis (serum ionized calcium, parathyroid hormone, and osteocalcin). (DEXA) method. Following the baseline evaluation adjuvant chemotherapy will be administered. The baseline measurements will then be repeated at 6, 12, and 24 months. At the 12 month evaluation women with chemotherapy-induced ovarian failure (approximately 70% of participants) will be randomly allocated to either one year of nasal spray calcitonin (200 IU/day) plus 1500 mg of oral daily calcium intake or nasal spray placebo plus 1500 mg of oral daily calcium intake in a double-blind placebo-controlled trial. Tamoxifen may also prevent bone loss and inhibit bone resorption. In Specific Aim #3 we will test whether tamoxifen prevents bone loss in breast cancer patients with chemotherapy-induced ovarian failure. In this observational study 42 premenopausal breast cancer patients with 0-3 axillary nodal metastases who receive adjuvant chemotherapy and tamoxifen will undergo the baseline evaluation and study evaluations at 6, 12, and 24 months. These prospective studies in premenopausal women with breast cancer will provide insights into the natural history of hemotherapy- induced ovarian failure and bone loss, and the effects of nasal spray calcitonin and tamoxifen in preventing the accelerated bone loss in these women.
CA60954	1999	Boston University	Case-Control Study of Dmpa and Breast Cancer	Breast Cancer	Etiology/Exogenous Factors in the origin and cause of cancer	DESCRIPTION: (Adapted from Applicant's Abstact). A large body of epidemiologic evidence suggests that estrogen is involved in the aetiology of breast cancer, but variables used a surrogates of estrogen levels, such as the age at menarche, are only weakly related to risk. Measured levels of endogenous estrogens also have generally been weakly related to risk, and it is not clear whether a single or even several measurements, over time, would be a good measure of cumulative estrogen exposure. Estrogens are strong determinants of BMD, which may, then, serve as a good measure of cumulative exposure. Recent evidence from studies of older women suggests that BMD may predict the risk of breast cancer. For example, in the Framingham Study, a relatively crude measure of bone mass from radiography was strongly related to the incidence of breast cancer; the rate ratio for the comparison of the highest to the lowest quartile of bone mass was 4.5. This application proposes to study the relation of BMD of the hip (neck of the femur) and the lumbar spine to the risk of breast cancer in a case-control study of breast cancer in relation to contraceptive use, currently being conducted in Cape Town, South Africa, among non-white women under the age of 55 years. In this study, extensive information is collected on risk factors for breast cancer. Cases and controls will be invited to have BMD measurements and will also be questioned about physical activity on the job, at home, and at leisure. The relative risk will be estimated for women with higher levels of BMD relative to women in the lowest quartile with control for important breast cancer and BMD risk factors. Female hormonesupplements are rarely used in this population and will not be confounders. Since the subject population is at low risk of breast cancer, a relationship between BMD and risk may show up more strongly than in higher-risk populations. If BMD at younger ages is a predictor of breast cancer risk, this would be useful for the identification of women at high risk at the ages at which American women often have BMD measured (i.e., at the time of menopause).
CA62345	1999	Dartmouth College	Womens Melanoma Risk--Reproductive and Hormonal Factors	Melanoma	Etiology/Exogenous Factors in the origin and cause of cancer	Studies of melanoma risk and use of female sex steroids and menstrual and reproductive events in women have yielded inconsistent results and have had insufficient sample size to address many important questions. To provide a more complete and precise assessment of these factors, we propose to pool data from 11 of the largest melanoma case-control studies completed to date. The data to be analyzed were collected through personal interviews with over 6,000 women (>2,500 cases and >3,500 controls). Specific hypotheses of interest include: 1) the potential risk of melanoma associated with long term oral contraceptive use, 10 or more years after first use, and 2) the effect of reproductive history, non- contraceptive hormones and surgical menopause on melanoma risk. We will use a uniform variable definition and coding scheme and apply a common analysis approach to each study individually. Next, a joint analysis will be performed using an innovative two-step approach. The investigative team will meet to review the results and to discuss their interpretation. Our approach will enable us to answer crucial questions regarding the role of female sex hormones on melanoma risk in a substantially more efficient and timely manner than undertaking a new study of this size.

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA63028	2001	University of California Los Angeles	Breast Cancer--Preparing for Survivorship	Breast Cancer	Cancer Control, Survivorship and Outcomes Research/Patient Care and Survivorship Issues	Breast cancer is the most common caner in women, with an estimated five year survival of 75%. As a result, the majority of female adult cancer survivors have had a breast cancer diagnosis. The literature describes a wide range of disruptions in day-to-day living as a result of a breast cancer diagnosis, with persisting problems of sexuality and intimacy in many survivors. The etiology of sexual dysfunction in breast cancer survivors has not been well-studied; however, it is likely to be multifaceted, and include such factors as pre-morbid sexual problems, changes in intimate relationships as a result of the breast cancer diagnosis and treatment, psychological problems leading to change in libido, as well as the physiologic consequences of chemotherapy and hormone therapy on endocrine function with resulting premature menopause and estrogen deprivation sequelae. This research will be conducted in two major metropolitan areas (Los Angeles and Washington, DC) and will use survey (N-1000) and face-to-face interview (N=150)approaches to describe the type, frequency and severity of sexual and intimate relationship problems in breast cancer survivors who are between one and five years since initial surgical treatment. The recruitment effort will be designed to over-sample African American breast cancer survivors, so that more can be learned about this understudied group. Using this survey data we will develop a predictive model to identify characteristics of breast cancer survivors who are at high risk for sexuality and intimacy problems. In the second phase of the research, we will survey a new sample of breast cancer survivors (N=1000) to validate the predictive model and to identify high risk subjects for participation in a randomized, controlled intervention study. A total of 310 breast cancer survivors will be randomized to the control of experimental condition, and will be recruited in three waves during an 18 month period. The intervention study will test the efficacy of a time-limited psychoeducational group program on improvement in emotional functioning as he primary outcome, with changes in sexual function, body image and intimate relationships as secondary endpoints. Representatives from national and local patient advocacy/breast survivor groups will serve as advisors to the research effort.
CA63369	2000	University of California Berkeley	Regulation of Mammary Cancer by Hormones	Breast Cancer	Etiology/Exogenous Factors in the origin and cause of cancer	Our overall goal is to determine the role of hormones and growth factors in the regulation of different phenotypes and oncogene activations in mouse mammary carcinogenesis. One out of nine women in the USA is likely to develop breast cancer during her lifetime. The etiology of breast cancer in women has not been defined. Epidemiological studies indicate that hormones are essential for the growth and differentiation of the breast as well as the development of breast cancer. Hormone related factors such as early age of menarche, late menopause, full term pregnancy at an early age, are associated with and increase or decrease in risk for breast cancer. Breast cancer is characterized as being heterogeneous in morphology, karyotypes, metastatic capabilities, hormone independence or hormone dependence and response to therapy. Taken together these characteristics provide circumstantial evidence that breast cancer must progress by a variety of pathways. The factors involved in the modulation of these cancer pathways have not been defined. We have developed a defined culture system in which the specific hormones present around the time of carcinogen exposure affect the incidence and type of mammary transformants as well as the molecular events that are associated with mammary carcinogenesis. Our working hypothesis is that the initiation of carcinogenesis is modulated by the mitogenic environment around the time of carcinogen treatment. We propose to study the role of hormones and growth factors in our defined culture system on the regulation of the phenotype and oncogene activation in mammary carcinogenesis. We will study the role of hormones and growth factors in regulating the expression of proto-oncogenes, the repair of DNA adducts, their role in selection of transformants, and the interaction of hormones and growth factors in carcinogenesis. Additionally we have cloned a novel transforming gene that is potentially another molecular probe for the analysis of sequential changes in carcinogenesis. Extensive molecular and biological characterization of the gene will be carried out.
CA63678	2000	University of Toronto	Risk Factor Analysis of BRCA1 and BRCA2 Carriers	Breast Cancer, Genital System, Female, Genital System, Male, Ovarian Cancer, Prostate Cancer	Etiology/Exogenous Factors in the origin and cause of cancer	DESCRIPTION: This is a collaborative group investigation to study the potential risks or preventive properties of exogenous hormones and prophylactic surgery for breast and ovarian cancer development in BRCA1 and BRCA2 carriers. The goals of this study are to: 1) identify families with BRCA1 and BRCA2 mutations; 2) establish whether oral contraceptive use protects against ovarian cancers in carriers of BRCA1 mutations; 3) establish whether tubal ligation protects against ovarian cancer in carriers of BRCA1 and BRCA2 mutations; 4) establish whether oral contraceptive use increases the risk of breast cancer in BRCA1 and BRCA2 mutation carriers; 5) establish whether hormone replacement therapy increases the risk of breast cancer in carriers of BRCA1 and BRCA2 mutations; 6) establish if oophorectomy is associated with a reduction in mortality from ovarian cancer in comparison to observational therapy; 7) establish if an oophorectomy reduces the risk of breast cancer; and 8) establish if a prophylactic mastectomy reduces the mortality from breast cancer in comparison to mammographic screening.

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA63731	2000	Center for Health Studies	Breast Cancer Surveillance in a Defined Population	Breast Cancer	Cancer Control, Survivorship and Outcomes Research/Surveillance	DESCRIPTION: (Applicant's Description) This proposed project takes advantage of comprehensive surveillance data on more than 100,000 women offered breast cancer screening through a program with mailed reminders to schedule mammography examinations within a managed care plan (Group Health Cooperative of Puget Sound, GHC). Cancer outcome (mortality, late-stage disease) for the target population are collected through a Surveillance, Epidemiology, and End Results reporting (SEER) registry and are linked to health care process data (service use, mammography assessments). This proposal includes 3 specific aims: 1) To continue breast cancer data system development at GHC to; a) improve data system software, enhance data storage capabilities, and facilitate data retrieval; b) incorporate new data components pertinent to research, such as a targeted survey; and c) maintain and improve data quality assurance, report generation, and data file development; 2) To use the data system to conduct 5 initiatives: a) The effect of short-term hormone replacement therapy (HRT) cessation on mammographic density; b) The likelihood of additional imaging (mammography and ultrasound) and the associated costs among women stopping HRT compared to women continuing or never using HRT; C) The factors that explain the reduced sensitivity of mammography among younger women; d) The biologic and other factors that influence the likelihood of late-stage disease; and, e) The effect of screening interval on stage at-diagnosis; and 3) To conduct 5 research projects related to screening mammography: a) The additional effect of mammographic breast density on the 5-year risk of breast cancer; b) Screening sensitivity and specificity by phase of menstrual cycle; c) The association between mammographic findings and cancer among women with "probably benign findings"; d) The effect of computer assisted reading on mammography interpretive performance; and e) Biomarkers associated with nodal metastases at-diagnosis among screened women. By continuing our multi disciplinary collaboration and using carefully designed prospective observational and evaluative studies the investigators will contribute to improvements in breast cancer screening, and the understanding of breast cancer biology.
CA66189	2000	New York University School of Medicine	Endogenous Estrogens and Endometrial Cancer	Endometrial Cancer, Genital System, Female	Etiology/Exogenous Factors in the origin and cause of cancer	This study will investigate the relation between postmenopausal endogenous levels of estrogens and subsequent development of endometrial cancer. In premenopausal women, estrogens unopposed by progesterone are known to stimulate endometrial cell division, providing a rationale for the role of estrogens in endometrial carcinogenesis. In postmenopausal women, estrogen replacement therapy is associated with an increased risk of endometrial cancer. However, there is no direct epidemiologic evidence that the physiologically low levels of endogenous estrogens observed after menopause are positively associated with endometrial cancer risk. In the face of increasing long-term use of estrogen replacement therapy, to prevent cardiovascular disease and osteoporosis, a better understanding of the role of endogenous estrogens may help develop prescription guidelines. The proposed study will use an existing resource of frozen serum samples collected between 1985 and 1991 in a cohort of 6071 postmenopausal women enrolled in a study of breast cancer and endogenous hormones (New York University Women's Health Study, NYUWHS). The specific aims of the proposal are: 1) to identify incident cases of endometrial cancer, using follow-up information generated by the NYUWHS until mid-1998; 2) to conduct a case-control study of endometrial cancer nested within this cohort. Sixty incident cases of endometrial cancer are expected to occur by the end of follow-up. For each case, four controls, matched on age and date of blood donation, will be selected. Controls will have to be alive, free of disease and with an intact uterus at time of diagnosis of the case. Information on known risk factors will be collected through telephone interviews. Serum samples will be assayed for estrone, estradiol, percent estradiol bound to sex hormone binding globulin and percent free estradiol. Conditional logistic regression for matched data will be used to assess whether higher levels of endogenous estrogens are associated with a higher risk of endometrial cancer. The study will also investigate whether the role of obesity in endometrial cancer can be explained by its action on endogenous estrogens.
CA72035	2001	Stanford University	Phytoestrogens and Colon Epithelium--A Randomized Trial	Colon and Rectal Cancer, Gastrointestinal Tract	Etiology/Exogenous Factors in the origin and cause of cancer	Diet and hormonal status are relevant to the etiology of colon cancer. The role of estrogens in the etiology of the disease has been strengthened considerably by the discovery that virtually all colonic tumors arise from epithelial cells that show hypermethylation of the estrogen receptor (ER) gene. Foods high in plant estrogens, (particularly soy isoflavones) are associated with reduced risk of colon neoplasia in epidemiologic studies. We hypothesize that isoflavones will lower risk of colorectal neoplasia by slowing or reversing the degree of methylation of the ER gene and by reducing colonic epithelial cell proliferation. We plan to test the hypothesis in a randomized, double-blind trial of isoflavone-rich and isoflavone-poor soy supplements. We further hypothesize that specific ER/estrogen responsive genes that are relevant to colon cancer will show a more controlled pattern in the presence vs. absence of isoflavones. A double-blind, randomized trial involving 160 individuals - 80 men, and 80 women not using hormone replacement therapy (HRT) - will be conducted. Eligible individuals with a recent history of adenomatous polyps, aged 50- 74, will be randomized (blocking on sex) to an isoflavone-poor soy supplement over a period of 12 months. Colonic biopsies (proximal and distal) will be taken at baseline and 12 months, and examined for degree of ER gene methylation, epithelial cell proliferation, and expression of specific estrogen-responsive markers - connexins (gap junction proteins), E-cadherin (a cell adhesion molecule), and bcl-2 and bax (an inhibitor and an inducer of apoptosis, respectively). Dietary compliance will be monitored by serum isoflavone concentration. We postulate that men and women in the isoflavone-rich arm will show a more favorable pattern of markers at 12 months than those on the placebo. Results from this human experimental study will provide important data on mechanisms of carcinogenesis and on possible preventive strategies in both sexes.

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA72099	2001	Duke University	Improving Cancer Risk Communication	Bladder Cancer, Breast Cancer, Lung Cancer, Respiratory System, Urinary System	Cancer Control, Survivorship and Outcomes Research/Behavior Related to Cancer Control	Major problems in cancer control are related, in part, to perceptions about cancer risk. These cancer control problems include smoking among African Americans and lack of adherence to mammography. In addition, risk perceptions affect women's decisions about whether to get mammograms and take estrogen replacement therapy (ERT). We propose to focus an outstanding group of Duke University investigators and a larger group of superb consultants on the vital topic of cancer risk communication. Never before has there been a concerted, comprehensive approach to cancer risk communication. Our goals are to develop a theoretical understanding of how people process risk information, develop and test population- sensitive measures of risk perception, develop useful techniques to improve risk comprehension and develop effective and cost-effective interventions to improve both decision making and cancer-related behaviors. As a result, we hypothesize that smoking will be reduced among African Americans and mammography use increased among women in their 50's and 60's. Moreover, we will improve decision making for mammography and ERT use. This CPRU includes three projects (one in which we will use biomarkers of genetic susceptibility to facilitate smoking cessation among African Americans, a study to facilitate informed decision making about ERT and a similar project on mammography), one developmental project (to develop an improved model of breast cancer risk prediction) and four cores (administration, biostatistics, cost-effectiveness and a risk laboratory), all developed with intentional synergy. All intervention projects include tailored print interventions and two will test the additional impact of telephone counseling, as well. All intervention-related data will be collected through telephone interviews. The use of core variables will permit comparisons across topics and populations. There will be sufficient African Americans and women to examine the effect of race and gender in these studies. We believe that this focused effort could lead to major advances in cancer control by developing the next generation of state-of-the-science interventions which will be grounded firmly in an understanding of cancer risk communication.
CA72554	1998	Washington University	Clinical & Psychosocial Factors in Breast Cancer	Breast Cancer	Cancer Control, Survivorship and Outcomes Research/Patient Care and Survivorship Issues	DESCRIPTION (Applicant's Description) Over the past 20 years, the management of primary breast cancer has evolved from a purely surgical treatment of the primary cancer to include acceptance of lumpectomy followed by radiation therapy and adjuvant therapy in many patients. The addition of postoperative chemotherapy and/or hormone therapy has improved overall survival in breast cancer patients. Depending on the type of therapy selected, patients may experience psychological trauma due to hair loss, weight gain, lethargy, and premature menopause. The psychological literature has focused principally on the impact of the primary surgery on the patient's quality of life and emotional adjustment. The additional psychological traumas related to adjuvant therapy have been insufficiently studied, to date. We propose to study the interrelationships amongst clinical, psychological, and social determinants of quality of life in women receiving adjuvant treatment for localized breast cancer. Changes will be studied at initiation of adjuvant therapy, and 2, 6, and 12 months after initiation of adjuvant therapy. For purposes of this proposal, quality of life includes: general quality of life, cancer specific quality of life, psychological adjustment, marital satisfaction, and sexual functioning. The needs for psychosocial support in these women change over the first year following localized surgical treatment of the primary cancer. We hope to systematically explore those changes to meet the following specific aims: 1. Develop an on-going needs assessment of support in coping with breast cancer and its treatment at key points during the first 12 months after surgery of the primary breast cancer. 2. Characterize the patient's changes in quality of life and related factors, including general quality of life, cancer-specific quality of life, psychological adjustment, marital satisfaction and sexual function during the 12 months following initiation of adjuvant therapy. 3. Characterize changes in clinical, psychological, and social influences on quality of life and related factors during the 12 months following initiation of adjuvant therapy. 4. Characterize changes in relationships, both new and old, as the patients' needs for clinical, psychological, and social support are altered during the 12 months after surgery for primary breast cancer. 5. Characterize how changes in clinical, psychological, and social support impact on the patient's outcome as measured by quality of life.
CA72787	2001	Fred Hutchinson Cancer Research Center	Calcium Channel Blockers in Breast Cancer Etiology	Breast Cancer	Etiology/Exogenous Factors in the origin and cause of cancer	DESCRIPTION: (Adapted from Applicant's Abstract). Although over one-third of all breast cancers are diagnosed among women aged 65-79 years, little epidemiologic research has specifically focussed on breast cancer in women of this age. Women of this age also commonly suffer from hypertension or coronary disease, and calcium channel blockers (CCBs) are often used to treat either of these conditions. Two recent studies, yet to be published, of women aged 65 and older, suggest that women who use CCBs may be at an increased risk of breast cancer. This suspected association is given biological plausibility by the observation that pharmacological blockade of the calcium channels can inhibit apoptosis (programmed cell death), the process whereby organisms eliminate unwanted cells (e.g., preneoplastic, initiated, damaged, excessive). In this sense, CCBs may be cancer promoters. The application proposes a case-control study of 1,000 women, aged 65-79, who reside in King County, Washington, who are on the Health Care Financing Administration (HCFA) tapes, and who are diagnosed with their first invasive breast cancer during the time period of January 1, 1997 through December 31, 1999. The personal interview responses of these women about drug use and other known risk factors for breast cancer will be compared to a control group of 1,000 women without breast cancer who will be identified through the HCFA tapes. Based on the preliminary studies and the evidence from in vitro studies on cells, it is posited that the use of CCBs increases the risk of breast cancer in older women. The plan is to assess whether calcium antagonists used in the treatment of hypertension and cardiovascular diseases promote breast cancer in women aged 65-79 years, and whether any one type of calcium channel blocker is more related to breast cancer than the other types. Since no studies have assessed present or past use of combined estrogen-progestin therapy in a large group of women this age, and the concurrent use of hormone replacement therapy (HRT) by these women may affect the proposed estimates of risk associated with CCBs, data will also be collected and analyzed on other drugs (viz., cimetidine, anti-depressants, lipid lowering drugs) frequently used by women in this age group.

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CA73638	2001	University of Illinois at Chicago	Biotransformation of Estrogen to Carcinogenic Quinoids	Breast Cancer, Endometrial Cancer, Genital System, Female	Biology/Cancer-Related Biology	There is a clear association between excessive exposure to estrogens and the development of cancer in several tissues including breast and endometrium. The risk factors for women developing these cancers are all associated with longer estrogen exposure; early menses, late menopause, and long term estrogen replacement therapy. The mechanism(s) of estrogen carcinogenesis is unknown. Estrogen metabolites can act as chemical carcinogens by binding to cellular proteins or DNA. The catechol metabolites of estrogens are oxidized to o-quinones which undergo redox cycling generating reactive oxygen species which can contribute to the carcinogenicity through oxidation of DNA. Our preliminary data also show that the o-quinones are converted to additional reactive alkylating agents, quinone methides. The focus of this proposal is the role of quinoid metabolites in estrogen carcinogenesis. The specific aims are: 1. Establish the role of quinoids in the carcinogenic and cytotoxic effects of estrogens. The carcinogenic potential catechol estrogens will be studied in C3H 10T1/2 cells and their ability to act as tumor promoters will be examined in JB6 cells. The cytotoxicity of estrogens and catechol metabolites will be investigated in human ovarian and breast cancer cell lines. Biochemical parameters which serve as indicators of redox vs. alkylation mechanisms will be determined. 2. Determine the importance of quinoid formation to the metabolism of estrogens. The contribution of the o-quinone/p-quinone methide pathway to the biodegradation of estrogens will be determined. The ability of P450 to oxidize estrogens and their metabolites to o-quinones will be studied. Unsaturated estrogens which are components of the estrogen replacement drug, Premarin, will be investigated to probe electronic and steric effects on the biotransformation of estrogens to quinoids. 3. Investigate the effects of quinoid structure on electrophilic and/or redox reactivity. The electrophilicity of quinoids will be determined by measuring their rates of reaction with deoxynucleosides and by examining the extent of DNA alkylation. Their redox ability will be assessed by measuring reduction potentials, monitoring changes in NADPH and GSH levels in microsomal incubations, measuring reactive oxygen species, and examining autoxidation rates of the catechols. These data will determine the role of quinoids in the carcinogenic effects of estrogens and provide a basis for the development of estrogen replacement drugs devoid of carcinogenic activity.
CA74415	2001	University of Utah	Genetic Epidemiology of Breast Cancer--BRCA1 and BRCA2	Breast Cancer, Genital System, Female, Genital System, Male, Ovarian Cancer, Prostate Cancer	Etiology/Exogenous Factors in the origin and cause of cancer	DESCRIPTION: (Adapted from the Investigator's Abstract) Many environmental, reproductive, and genetic factors have been associated with an increased risk of breast and ovarian cancers. A family history of breast cancer has been identified as a major risk factor for the development of the disease. A genetic predisposition likely accounts for 5 to 10 percent of breast cancer and ovarian cancer. Approximately 80 percent of inherited early onset breast cancer is attributed to the breast cancer genes, BRCA1 and BRCA2. Among families with the same BRCA1 (BRCA2) mutations, there are differences in age-specific penetrance, lifetime penetrance, proportions of breast and ovarian cancer, and risks of other cancers. This variability suggests there are environmental and genetic factors interacting with the BRCA1 and BRCA2 genes. The identification of predictors of phenotypic expression, not only in terms of type of cancer but also in modulating age at onset, has implications for screening and prevention strategies for women at significantly increased risk of breast and ovarian cancers due to the BRCA1 and BRCA2 genes. This is a proposal to examine the effects of reproductive and genetic factors which may modulate the incidence by age and overall incidence of breast and ovarian cancers in individuals with BRCA1 and BRCA2 mutations. The cohort is composed of Caucasian and African American BRCA1 and BRCA2 mutation carriers. We have already sampled 215 BRCA1 and 141 BRCA2 mutations carriers in our Utah kindreds and will continue to sample within these families to identify all mutation carriers. Little information is available regarding prevalence of BRCA1 and BRCA2 in African Americans, although for women less than 44 years of age, their incidence of breast cancer is higher than for Caucasians. With collaborators in Dallas and Chicago, we propose to contact African American families with a history of breast and/or ovarian cancer, to identify BRCA1 and BRCA2 mutations, and sample within those families to identify all mutations carriers. The cofactors to be examined in this cohort include ages at menarche and menopause, parity, age at first pregnancy, use of oral contraceptives, and hormone replacement therapy. The genetic factors to be investigated include the h-RAS VNTR and carcinogen metabolizing genes GSTT1, GSTM1, CYP2D6, CYP1A1, and EPHX. Survival analysis models will be used to estimate cumulative incidence by age and overall incidence for breast and ovarian cancers stratified by the hormone, reproductive, and genetic factors.
CA76017	2001	University of North Carolina Chapel Hill	HRT and Changes in Mammographic Density	Breast Cancer	Etiology/Exogenous Factors in the origin and cause of cancer	DESCRIPTION: Breast parenchymal patterns are depicted on mammograms as variations in radiographic density, which correspond to the relative amounts of fatty tissue (c.f., epithelial and stromal tissues). Mammographic density is highest in women with the greatest proportion of epithelial, stromal and connective tissues. Compared to no density, high density (>50%) has been consistently associated with significantly elevated long-term breast cancer risk, independent of age, menopausal status, or other breast cancer risk factors. Recently, several small case series have suggested that postmenopausal HRT may increase density in some postmenopausal women, although selection biases and imprecise measurement of exposure and outcomes (density) detract from the validity of these results. Given the small but persistent association of HRT with increased risk of breast cancer, and the increasing prevalence of HRT use among postmenopausal women, assessing the magnitude and correlates of the effect of HRT on mammographic density may contribute to improved understanding of the aetiologic role of exogenous hormones and to public health breast cancer prevention efforts. The objectives are to: 1) reliably estimate the quantitative effect of HRT on mammographic density in postmenopausal women; and 2) determine whether HRT-related density changes differ by ethnicity, age, time since menopause, body mass, or other breast cancer risk factors. This research is ancillary to the WHI, a long-term, multi-center, randomized trial of HRT in postmenopausal women. WHI participants are assigned to HRT (estrogen only for hysterectomized women, or combined progestin-estrogen for women with a uterus) or placebo. Working with the WHI clinical centers, measurements will be made of the percentage of breast density on participants' mammograms taken at baseline, one-year and two-year follow-up intervals, and then compared for longitudinal density change among treatment groups. The sample is comprised of 1200 women with adequate numbers in four ethnic groups: European, African, Hispanic and Asian/Pacific Islander Americans.

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CA76366	2001	Fred Hutchinson Cancer Research Center	Hormone Replacement Therapy and Large Bowel Cancer Risk	Colon and Rectal Cancer, Gastrointestinal Tract	Biology/Cancer-Related Biology	The benefits and risks of estrogen replacement therapy continue to confuse women and their physicians. Recent evidence suggests that estrogen replacement may be associated with reductions in large bowel cancer, a common disease among postmenopausal women. Further study of this potentially important association would provide more precise estimates of the magnitude of effect, identify salient patterns of use, and, importantly, supply insights into the biology of this tumor in women. A population-base case-control study is proposed to evaluate the association between postmenopausal hormones and the occurrence of colorectal cancer. This study will specifically assess use of estrogens with and without progestin, the duration and currency of hormone use, and inter-relationships with body mass. Additional aims of this study are to elucidate the mechanisms of this inverse association, specifically the relationship of HRT to hormone receptors and proliferation in the bowel, and to examine the modifying role of more common cancer susceptibility genes influencing the metabolism of estrogens. Over a three year period, interviews will be conducted with 1,100 women with newly diagnosed cancer of the colon or rectum selected from the population. In addition to the structured telephone interview, fixed diagnostic tissue will be obtained from 540 case in order to evaluate estrogen-receptor status and proliferation markers. Blood samples on a sample of 600 (most with diagnostic tissue) cases and 600 controls will be obtained for genetic studies of polymorphisms relevant to estrogen metabolism and function, specifically CYP17 and the estrogen receptor gene. The proposed study and its extensions should provide clear evidence for the degree to which HRT is protective against colorectal cancer and permit the determination of some of the relevant pathways for that protection.
CA77037	1999	Keystone Symposia	Conference on Breast and Prostate Cancer	Breast Cancer, Genital System, Male, Prostate Cancer	Etiology/Interactions of Genes and/or Genetic Polymorphisms with Exogenous and /or Endogenous Factors	DESCRIPTION: (Applicant's Description) New and exciting advances have been made in the delineation of 1) genetic alterations which predispose to and/or cause breast and prostate cancer, 2) novel molecular mechanisms of hormone action, such as delineation of steroid receptor co-regulators, identification of novel steroid receptors, steroid hormone receptor interactions with membrane initiated signal transduction pathways, 3) identification of environmental hormone mimetics and novel mechanisms by which they may impact on growth and function of normal and cancerous breast and prostate. Since the growth and function of both normal breast and prostate are hormone dependent and their respective cancers are hormone responsive, delineating the roles and mechanisms of action of hormones is pivotal for progress in cancer etiology, prevention and therapy. Breast cancer and prostate cancer share many features: they are the most commonly diagnosed cancers in American women and men, respectively; both are regulated by sex steroids; both develop hormone independence; both have a hereditary component; both organs have a tubuloalveolar architecture; and for both organs, stromal-epithelial interactions play an important role in tissue morphogenesis and growth control. The goal of the proposed Keystone Symposium on Breast and Prostate Cancer is to provide a multidisciplinary program that addresses key questions and presents novel information about: 1) what are the mechanisms of action of endogenous hormones/growth factors and the role of exogenous hormones (hormone replacement therapy and/or environmental hormones) in etiology and progression of cancer 2) what is the interaction between hormones and gene mutations in carcinogenesis and 3) how can this knowledge be exploited to develop novel strategies for cancer prevention and therapy. It is expected that the knowledge shared and ideas generated will identify new directions for future endeavors and that bringing together researchers working on prostate and breast will have a synergistic impact on breast and prostate cancer.
CA77398	2001	Public Health Institute	Breast & Other Cancer in the California Teachers Cohort	Breast Cancer	Etiology/Resources and Infrastructure Related to Etiology	DESCRIPTION (adapted from applicant's Description): A cohort of 133,000 California school teachers has been established by a collaborative group of epidemiological investigators with the goals of evaluating unresolved issues related to breast cancer risk factors and studying other important issues related to women's health. The teachers were recruited with a detailed multiple choice, optically-scanned mail survey. Scanning of the questionnaires has been completed and data editing is ongoing. Planned follow-up includes routine linkage with the California Cancer Registry and California mortality files, annual re-contact of cohort members for follow-up, and biennial contact for collecting additional risk factor exposure data and information on other health outcomes. The Specific Aims for this project are to: 1) test a series of unresolved and emerging hypotheses related to breast cancer aetiology (specifically associations with the lactation, hormone replacement therapy, abortion/miscarriage, dietary phytoestrogens, fibre, micronutrient consumption, alcohol intake, physical exercise and activities, family history of breast and other cancers, and active and passive cigarette smoke exposure); 2) conduct calibration/validation studies of the food-frequency questionnaire and self-reported information on family history of breast and other cancers reported in the baseline questionnaire; and 3) follow this cohort for five additional years, during which time, two or more questionnaires will be mailed to update initial exposure assessments, collect new exposure information, and assess additional disease outcomes for testing novel hypotheses of major importance to women's health, in a timely manner. During the next five years, 2,025 invasive incident and 390 in situ incident breast cancers are anticipated which will provide ample statistical power to address each of the proposed hypotheses in detail. The California Teachers Study presents a rare opportunity to study women's health, because of the size of the cohort, the uniformly high level of education among teachers, their experience with survey instruments, their diversity of exposures and geographic residences, and the relative ease with which they can be followed in California. This research is intended to substantially increase knowledge of preventable risk factors for cancer and other health outcomes.

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CA77596	2001	University of Pennsylvania	Molecular Susceptibility to Hormone Induced Cancer	Breast Cancer, Endometrial Cancer, Genital System, Female	Etiology/Endogenous Factors in the origin and cause of cancer	There is strong evidence that a combination of inherited genotypes and hormone exposures influenced breast cancer risk. Furthermore, inherited genotypes involved in the metabolism of steroid hormones may also modify a woman's risk of developing breast cancer. Knowledge about interactions of these factors in breast cancer etiology may improve the ability to identify women at increased breast cancer risk. This knowledge may in turn be used to target women for breast cancer prevention or treatment strategies. We propose a population-based case-control study that will directly address the complex, multi-factorial etiology of breast cancer that involves the interaction of genotypes and hormonal risk factors. These hormonal factors include endogenous exposures measured by parity-related events, and exogenous exposures to compounds such as estrogen replacement therapy (ERT). This study will address a number of specific hypothesis. First, we will evaluate whether candidate susceptibility genotypes are associated with breast cancer in a case-control analysis. The genes of primary interest will be CYP1A1, CYP3A4, and glutathione-S-transferase mu and theta genes, which are involved in the metabolism of steroid hormones. Second, we will evaluate whether genotypes and other reproductive risk factors interact in breast cancer etiology, and whether knowledge of genotypes will improve our understanding of breast cancer etiology once hormonal risk factors (e.g., reproductive history or ERT) are known. Third, we will evaluate whether the genetic and hormonal etiology of breast cancer differs by race. In order to address these hypotheses, we will undertake a study in the Greater Delaware Valley using an existing network of hospitals to identify a population-based sample of cases and random digit dialed controls. The sample will consist of 1200 White and 1200 Black subjects. Risk-factor information will be obtained from a telephone interview, a biosample containing DNA will be collected using a non-invasive cheek swab method. and pathology information will be collected using standardized medical record abstraction. Analyses will be undertaken to evaluate the roll of candidate genotypes and hormonal risk factors in breast cancer etiology by race. These analyses will allow us to examine genotype by hormonal interactions in breast cancer etiology.
CA77617	2000	Mayo Clinic Rochester	Expression of Cyclin E in Gynecologic Malignancies	Genital System, Female, Ovarian Cancer	Biology/Cancer-Related Biology	DESCRIPTION: (Adopted from the application)The cyclins and their catalytic partners, cyclin-dependent kineses (Cdks) are key regulators of the cell cycle. Overexpression of cyclin genes has been described in several forms of human cancers. Preliminary evidence suggests that cyclin E is expressed in a subset of gynecological cancers, namely clear cell carcinoma of the ovary, endometrium and cervix. The first specific aim will focus on confirming the specificity of cyclin E for clear cell tumors of Mullerian origin. Expression of cyclin E will be assessed in different histological subtypes of epithelial ovarian, endometrial, cervical and renal cancers. Cyclin E specificity for gynecologic clear cell carcinomas may provide a useful diagnostic marker to help distinguish a pelvic tumor of Mullerian versus non-Mullerian origin. This may have important implications in cases when the primary lesion is unknown since the therapy for ovarian and renal malignancies differs. Histological subtype specific aberrations in cyclin/Cdk expression may be important implications in the potential success of future therapies targeting Cdks. The first generation of these inhibitors are being evaluated in clinical trials. The second specific aim will evaluate steroid hormonal regulation of cyclin E using an in vitro model. The effects of estrogen and progesterone on cyclin E activity will be assessed using an ovarian cancer cell line. Increasing evidence suggests a role for hormones in the etiology of gynecologic malignancies. Moreover, cyclins have been shown to be regulated by estrogen and progesterone in breast cancer cell lines. The role of hormones in the development of reproductive tract cancer has important implications in the treatment of menopause and may also contribute to the direction of future therapeutic and preventative agents. Specific aim three will evaluate the expression and activity of cyclin dependent kinase inhibitors in order to elucidate the mechanism of aberrant cyclin E activity. The activity of a cyclin/Cdk is dependent upon the association with cyclin dependent kinase inhibitors (CdkIs). This specific aim will attempt to correlate cyclin E activity with the CdkIs, p2 1 and p27 in gynecologic malignancies. In addition, the role of estrogen and progesterone on CdkI association with cyclin E will be determined. Interestingly, it appears that the increase cyclin E activity in breast cancer cell lines in response to steroid hormones is mediated through alterations in the Cdk-inhibitory proteins. Understanding the mechanisms of cyclin E aberrations may lead to powerful and convenient models for studying potential tumor promoters, markers and antiproliferative agents.

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CA77708	2001	University of California Los Angeles	Sex Steroids and Mammogram Density in the Postmenopause	Breast Cancer	Etiology/Endogenous Factors in the origin and cause of cancer	DESCRIPTION: (Adapted from Investigator's Abstract) Epidemiologic studies find that increased mammographic density is an independent risk factor for breast cancer and the magnitude of risk associated with mammographic density is greater than that associated with almost all other known risk factors for breast cancer. This application focuses on 3 major questions: 1) are endogenous levels of sex steroids in postmenopausal women related to mammographic density; 2) does treatment with postmenopausal estrogen and estrogen/progestin therapy increase mammographic density; and 3) do the serum levels of estrone achieved as a result of treatment with postmenopausal hormone therapy predict change in mammographic density? To address these questions, the amount of density of mammograms performed during the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial will be determined using a computer-based threshold technique. PEPI was a 3-year, randomized placebo controlled trial of conjugated equine estrogens (CEE) vs. CEE plus one of 3 progestin regimens, which enrolled 875 postmenopausal women aged 45-64 at baseline. Data already collected as part of PEPI that will be used in this project will include: endogenous sex steroids at baseline, PEPI treatment assignment, estrone serum levels on-treatment, and necessary covariates. The project will last 3 years and take place at 3 sites: UCLA, USC, and Bowman Gray. The specific aims are to: 1) measure the density of mammograms performed at baseline and 12 months; 2) determine whether baseline mammographic density is associated with endogenous levels of sex steroids; 3) quantify the relation between change in mammographic density and adherence to treatments; and 4) determine whether changes density are associated with serum levels of estrone achieved as a result of hormone therapy. By assessing density changes in mammograms with this computer-based method, which has been previously linked to a quantified increase in risk of breast cancer, it may be possible to assess how much of a risk-increase would be predicted by hormone use. The investigators state that this may serve as the first in a series of investigations that would allow identification of those women at higher risk of developing breast toxicity from postmenopausal supplemental hormone use.
CA78549	1999	University of Kansas Medical Center	Third International Symposium on Hormonal Carcinogenesis	Breast Cancer, Genital System, Female, Genital System, Male, Ovarian Cancer, Prostate Cancer	Biology/Cancer-Related Biology	DESCRIPTION (Applicant's Description) The International Symposia on Hormonal Carcinogenesis have become the premier international forum for both USA and foreign researchers studying the role of hormones and other growth regulators in the initiation, promotion, and progression of hormonal cancers. Many of these neoplasms, namely, breast, prostate, ovarian, and endometrial, represent some of the most prevalent cancers Occurring in humans. These Symposia are unique in that they bring together a group of epidemiologists, basic scientists, and clinicians of widely diverse disciplines, including cell and molecular biology, endocrinology, biochemistry, reproductive toxicology, pathology, gynecology, medicine, and epidemiology. Invited speakers are engaged in the cutting edge of hormone-associated cancer research. The Third Symposium will be held in cooperation with the Fred Hutchinson Cancer Research Center and will take place in its facilities in Seattle, WA, September 6-12,1998. Major sessions include: (1) Population/molecular epidemiologic studies of breast, prostate, and ovarian cancers; (2) Molecular genetic studies of hormonal cancer sites; (3) Estrogen receptor interactions in human and animal models; (4) Estrogen/progesterone action in breast cancer; (5) Cell cycle and cell proliferation studies in breast and endometrial cancers; (6) Oncogenes and suppressor genes; (7) Aromatase: Implications for breast cancer; and (8) Organ sites: Prostate and ovary. Symposium and State-of-the-Art lectures will be presented by outstanding investigators on subjects pertinent to hormonal carcinogenesis. The clinical session will focus on the benefits and risks of hormone and estrogen replacement therapy (HRT, ERT) in women. Both basic and clinical studies will be presented in this session. Because of the comprehensive and integrated format, these Symposia have become the sole international forum for dissemination of the latest advances in the field, providing a wider exposure of information by the timely publication of the proceedings in book form.
CA79024	2001	Sloan-Kettering Institute for Cancer Res	Premature Menopause in Survivors of Childhood Cancer	Breast Cancer, Genital System, Male, Not Site-Specific Cancer, Prostate Cancer	Cancer Control, Survivorship and Outcomes Research/Patient Care and Survivorship Issues	There is strong evidence that a combination of inherited genotypes and hormone exposures influenced breast cancer risk. Furthermore, inherited genotypes involved in the metabolism of steroid hormones may also modify a woman's risk of developing breast cancer. Knowledge about interactions of these factors in breast cancer etiology may improve the ability to identify women at increased breast cancer risk. This knowledge may in turn be used to target women for breast cancer prevention or treatment strategies. We propose a population-based case-control study that will directly address the complex, multi-factorial etiology of breast cancer that involves the interaction of genotypes and hormonal risk factors. These hormonal factors include endogenous exposures measured by parity-related events, and exogenous exposures to compounds such as estrogen replacement therapy (ERT). This study will address a number of specific hypothesis. First, we will evaluate whether candidate susceptibility genotypes are associated with breast cancer in a case-control analysis. The genes of primary interest will be CYP1A1, CYP3A4, and glutathione-S-transferase mu and theta genes, which are involved in the metabolism of steroid hormones. Second, we will evaluate whether genotypes and other reproductive risk factors interact in breast cancer etiology, and whether knowledge of genotypes will improve our understanding of breast cancer etiology once hormonal risk factors (e.g., reproductive history or ERT) are known. Third, we will evaluate whether the genetic and hormonal etiology of breast cancer differs by race. In order to address these hypotheses, we will undertake a study in the Greater Delaware Valley using an existing network of hospitals to identify a population-based sample of cases and random digit dialed controls. The sample will consist of 1200 White and 1200 Black subjects. Risk-factor information will be obtained from a telephone interview, a biosample containing DNA will be collected using a non-invasive cheek swab method. and pathology information will be collected using standardized medical record abstraction. Analyses will be undertaken to evaluate the roll of candidate genotypes and hormonal risk factors in breast cancer etiology by race. These analyses will allow us to examine genotype by hormonal interactions in breast cancer etiology.

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA80625	1999	Yale University	Menopausal Symptom Relief for Women with Breast Cancer	Breast Cancer, Genital System, Female, Ovarian Cancer	Treatment/Complementary and Alternative Treatment Approaches	The proposed randomized, placebo-controlled clinical study will examine the use of acupuncture for menopausal symptom management for women who experience menopause following treatment for breast cancer. The study is designed to: 1) Test the anticipated treatment benefit for menopausal symptom relief using changes in frequency and severity of hot flashes as outcome measures; 2) Explore the anticipated treatment benefit of acupuncture for menopausal symptom relief using changes in severity of mood changes, sleep disturbances, loss of concentration, joint pain, headache and nervousness as well as changes in luteinizing hormone (LH), follicle stimulating hormone (FSH) and quality of life; 3) Determine the feasibility of the treatment strategy and develop realistic protocols for women previously diagnosed and treated for breast cancer by examining recruitment and retention rates and through exit interviews regarding the potential burden associated with symptom frequency and severity ratings and acupuncture sessions. A three group design (site specific needling, control needling, usual care) will be used. Acupuncture treatment will take the form of either menopausal specific acupuncture sites or control needling at acupuncture points identified in the literature as irrelevant to the symptoms associated with menopause. The non acupuncture control group will receive usual care with standardized educational information drawn from published menopausal literature concerning non-hormonal menopausal symptom management strategies. The study variables are Menopausal Symptoms with hot flashes (primary marker), mood changes, sleep disturbances, loss of concentration, joint pain, headache and nervousness as measured by the daily Symptom Diary and modified Kupperman Index; Physiological Measures of menopausal status (serum LH and FSH); Quality of Life as measured by The Menopause Specific Quality of Life Questionnaire; and Protocol Design as measured by recruitment and retention rates and exit interviews. A convenience sample of 81 women who experience menopausal symptoms within one year following treatment for Stage I or II breast cancer will be recruited. Data analysis includes descriptive statistics, repeated measures ANOVA, time series analysis and content analysis. Results from the study will test the effectiveness of acupuncture as a treatment for menopausal hot flashes and inform the design of a larger randomized, placebo-controlled clinical trial of acupuncture for menopausal symptom relief.
CA80636	2000	Fred Hutchinson Cancer Research Center	Endometrial Cancer and CYP1A1, GSTM1 and Polymorphisms	Endometrial Cancer, Genital System, Female	Etiology/Endogenous Factors in the origin and cause of cancer	DESCRIPTION: (Applicant's Description) Women who smoke cigarettes have about half the risk of endometrial cancer of non-smokers. Female smokers have been observed to have an increase in 2-hydroxylation of estrogens, and this increased 2-hydroxylation has been suggested as a mechanism to explain the apparent antiestrogenic effect of cigarette smoke. Polymorphisms in several genes involved in metabolizing potential carcinogens in cigarette smoke have been related to an increased risk of lung cancer. One of these genes is also involved in 2-hydroxylation of estrogens. Thus, it might be anticipated that women who have the high-risk genotypes, in terms of lung cancer, would have a reduced risk of a condition such as endometrial cancer, whose incidence is reduced by cigarette smoking. However, in a recent small case-control study, a strong, positive relationship between the presence of some of the polymorphisms in these genes and endometrial cancer risk was reported. In our proposed population-based case-control study, we will explore whether polymorphisms in some of these genes are associated with endometrial cancer risk. The genes of interest are: cytochrome P450 1A1 (CYP1A1), glutathione-S-transferases M1 (GSTM1) and T1 (GSTT1), and catechol-O-methyltransferase (COMT). Cases and controls will be drawn from our funded study of continuous combined hormone replacement therapy and endometrial cancer. Cases are women ages 50-69 years with incident endometrial cancer diagnosed between 6/l/97 and 7/31/00, who reside in western Washington. Controls are women recruited through random-digit dialing (ages 50-64 years) and Health Care Financing Administration files (ages 65-69 years), who reside in the same geographic area. In the proposed study, 175 cases and 175 controls will be asked to provide a blood specimen at the time of interview. Using purified DNA from these blood samples, the genotypes of interest will be assayed using PCR and RFLPs. Differences in the distributions of genotypes between cases and controls will be assessed in the whole study population, as well as in sub-groups of women defined by cigarette smoking history and use of hormone replacement therapy (HRT). Since endometrial cancer is strongly hormone-related, the results of this study could have relevance for other, more common cancers whose relation to hormones is not so straightforward. Additionally, this information potentially could be used to predict a woman's sensitivity to the carcinogenic effects of HRT, and thus bear on a woman's decision regarding long-term use of HRT.
CA80888	2001	Dartmouth College	Hormone Replacement Therapy and Breast Cancer	Bone Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma, Breast Cancer	Etiology/Exogenous Factors in the origin and cause of cancer	No abstract available for this Project.ID.

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA81220	2000	Case Western Reserve Univ-Henry Ford Hsc	Colon Cancer Survivors--Medications & Risk of Recurrence	Colon and Rectal Cancer, Gastrointestinal Tract	Cancer Control, Survivorship and Outcomes Research/Patient Care and Survivorship Issues	DESCRIPTION (Adapted from the Applicant's Abstract): Colorectal cancer will be diagnosed in over 129,000 Americans in 1999. To combat this disease, new avenues to decrease the risk of colorectal cancer, such as chemoprevention, are being explored by researchers. Non-steroidal anti-inflammatory drugs (NSAIDs) and hormone replacement therapy (HRT) have been shown to decrease incident colon cancer. Little is known of their effect on persons with a history of colon cancer which, fortunately, is a continually expanding population as survival has been significantly improving over the last twenty years. The objective of this epidemiologic study is to determine whether NSAIDs or HRT is associated with recurrence or survival among individuals diagnosed with colorectal cancer. The proposed research will establish a cohort of colorectal cancer patients treated with curative intent and create a comprehensive longitudinal database, including data on the ascertainment of subsequent adenomatous polyps, colorectal cancer and survival. The specific aims are: (1) to determine whether NSAID use deceases the risk of recurrence of colorectal cancer; (2) to determine whether HRT use deceases the risk of recurrence of colorectal cancer; (3) to determine whether NSAID use affects short-term survival; and (4) to determine whether HRT use affects short-term survival. The cohort will be established from colorectal cancer patients enrolled in two managed care organizations, Health Alliance Plan (Detroit, MI) and Health Partners (Minneapolis, MN). Cohort subjects will be followed for at least five years for new evidence of disease, recurrence and survival outcome. Using automated pharmacy data, the timing of use and exposure to NSAIDs and HRT will be analyzed among cancer survivors, along with potentially confounding variables, in relation to these outcomes.
CA81243	2001	Wadsworth Center	Carcinogenicity of B Ring Unsaturated Estrogens	Breast Cancer	Biology/Cancer-Related Biology	The major concern regarding estrogen replacement therapy (ERT) is the significant increase in the risk of breast cancer that accompanies long-term use. The most commonly used formulation for ERT is Premarin, a preparation consisting largely of B-ring unsaturated estrogens including conjugated forms of equilin (Eq) and equilenin (Eqn). Our preliminary studies show Ah-receptor-regulated metabolism of Eqn to 4-hydroxylated metabolites in several human breast-derived cell lines expressing cytochrome P4501B1 (CYP1BI). Semiquinones and quinones derived from these 4-hydroxy metabolites, which are adductive and lead to free radical production, may be involved in carcinogenesis. We hypothesize that estrogens are involved in both the initiation and promotion phases of carcinogenesis, and that aromaticity of the B-ring of steroidal estrogens increases carcinogenic potency. Our broad, long-term goal is to determine whether steroidal estrogens, including the B-ring unsaturated estrogens, Eq and Eqn, are carcinogenic through metabolic activation via catechol estrogens. 0ur Specific Aims are to: 1) Characterize Eq and Eqn metabolism in a series of immortalized tumor- and non-tumor-derived human breast-cell lines. Pathways of Eq and Eqn bioactivation involving hydrolysis of conjugates, reduction to 17beta-dihydro forms and hydroxyation to catechol estrogens will be investigated. 2) Determine the catechol synthetic activities of human cytochromes P450 of the CYP1, CYP2, and CYP3 families with Eq, Eqn, and their 17alpha- and 17beta-dihydro forms as substrates. 3) Establish transgenic mouse lines expressing human CYP1B1 in the mammary epithelium, 4) Determine the effects of treatment with Eq and Eqn on DNA damage and the incidence of mammary-gland tumors in human CYP1B1-transgenic mice. The studies described here will provide novel results regarding the metabolism of the B-ring unsaturated estrogens by human enzymes in breast epithelial cells, and may provide mechanistic data supporting a role of metabolic activation of Eq, Eqn, and endogenous in the initiation of carcinogenesis in the human breast.
CA82091	2001	Mayo Clinic Rochester	Serologic Serbbl in Healthy Women	Genital System, Female, Ovarian Cancer	Etiology/Endogenous Factors in the origin and cause of cancer	Epithelial ovarian cancer (EOC) is the leading cause of death from gynecologic malignancies in the United States. EOC usually is not diagnosed until a late stage, which results in a poor prognosis for the patient. Cost-effective, sensitive and specific screening methods to identify women who are at risk of developing EOC, and to detect early stages of EOC are, therefore, urgently needed. Multi-parity, lactation, and oral contraceptive use are known to decrease a woman's risk of EOC. These factors are believed to decreased the probability of cellular transformation by suppressing ovulation, wound healing, and proliferation of ovarian surface epithelium by altering gonadotropic and steroid hormone levels. Gonadotropic and steroid hormones regulate the expression of the erbB proto-oncogene receptor tyrosine kinases family. ErbB receptors play an important role in regulating the normal growth and differentiation of epithelial cells. Moreover, ErbB1 receptors are commonly amplified and/or over-expressed in ovarian neoplasms of epithelial origin, where increased signaling may contribute to cellular transformation. In addition to full-length ErbBI receptors, normal and malignant tissues produced "soluble" ErbB1 (sErbB1) analogs that have growth inhibitory properties in vitro. Recently, we have shown that serum sErbB1 levels differ significantly between healthy men (median = 24,512 fmol/ml) and women (median = 3,716 fmol/ml). Furthermore, studies with stage III or IV EOC patients indicate that serum sErbB1 levels are significantly lower in patients with this disease relative to healthy, age-matched women. Thus, decreased serum sErbB1 may contribute to the etiology of EOC. These observations have led us to hypothesize that decreased serum sErbB1 levels may be a risk factor for developing EOC and/or a potential diagnostic tumor biomarker of EOC. Since steroid hormones regulate erbB gene expression, and pregnancy, lactation, and oral contraceptive use affect circulating gonadotropic and steroid hormone levels, we predict that serum sErbB1 levels will be associated with aspects of a woman's reproductive history. The specific aims of this proposal are, therefore, to conduct a study of serum sErbB1 levels in healthy women: 1) during their menstrual cycle, 2) during oral contraceptive use, 3) during pregnancy, 4) during lactation, and 5) following menopause. This pilot project will establish baseline values for serum sErbB1 levels in healthy women, thereby, allowing us to obtain the information necessary to test the above hypotheses in future studies.

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA83114	2001	Karolinska Institute	Genetic Susceptibility to Hormonal Carcinogenesis	Breast Cancer, Endometrial Cancer, Genital System, Female	Etiology/Endogenous Factors in the origin and cause of cancer	Causes and mechanisms involved in the development of most cancers are not well known. As for breast and endometrial cancers, most risk cancers indicate that sex hormones are important. However, hormone-related factors-like nulliparity, late age at first birth, early menarche, late menopause, long-term use of oral contraceptives or hormone replacement therapy-together with first-degree family history, explain only half of all breast cancers occurring. Further, in the presence of a high-risk factor, the added absolute risk is usually small. For instance, hormone replacement therapy (HRT) for many years confers an attributable risk increase of only about one percent. It is likely that some individuals are at higher susceptibility of hormonal carcinogenesis. Interest is now focusing on inherited variations in life-time exposures to estrogens in target organs. The proposed study aims to explore the hypothesis that functional polymorphisms of the gene for the CYP1B1 and COMT enzymes entail different activity levels, for metabolic activation of estradiol to reactive catechol estrogens, and for clearance of such genotoxic compounds, respectively. Specifically, a high-activity allele of the CYP1B1 gene may increase the risk of breast endometrial cancer by increasing the load of genotoxic metabolites, or conversely a low-activity allele may enhance the riskthrough higher levels of estradiol that increase proliferation; the lowest activity allele of COMT is the most adverse through a low capacity to clear genotoxic metabolites. The study will be conducted among subjects who participated in two coordinated population-based case-controls studies, in which information on risk factors for breast and endometrial cancer was collected through questionnaires. From these two parent studies, 1200 breast cancer cases (out of 3900), all 800 endometrial cancer cases, phenotypically well characterized-and 1300 coordinated control subjects (out of 4200) are being enrolled in molecular epidemiological studies. These concern associations between selected ER, VDR, and AR gene polymorphisms and the risk of cancer in the breast and endometrium. The same data base will be used for the proposed study. After informed consent, the majority of the women (75%) donate blood and an small proportion of the case subjects (5%) allow use of archived specimens (also for deceased cases) for production of DNA. In this study, DNA will be genotyped for high and low activity alleles of the CYP1B1 gene, recently shown to be functionally polymorphic, and for three different activity alleles of the COMT gene. These alleles will be analyzed, with the highest statistical power hitherto, as risk factors singly, jointly and in subgroups of women with respect to risk factors. This research is innovative by examining for the first time how variants of genes for enzymes involved in estrogen metabolism affect the risk for two of the most important hormone-related cancers in women. It gives prospects for better definition of individual susceptibility and thereby a possibility for selective advice and improved cancer prevention.
CA83849	2000	University of Pennsylvania	Hunk and Punc Function in Mammary Epithelial Biology	Breast Cancer	Cancer Control, Survivorship and Outcomes Research/Patient Care and Survivorship Issues	DESCRIPTION: The loss of growth control characteristic of carcinogenesis is uniformly accompanied by alterations in normal pathways of differentiation and development. This implies an intrinsic relationship between these processes. The existence of endocrine risk factors for breast cancer that are related to the timing of normal developmental events such as menarche, menopause and age at first full-term pregnancy epitomizes the relationship between development and carcinogenesis in the breast. Understanding the mechanism by which reproductive events influence breast cancer susceptibility will undoubtedly require a far better understanding of normal mammary development than currently exists, particularly with respect to identifying the genes that control proliferation and differentiation. Since major insights into the molecularmechanisms of differentiation, development, and carcinogenesis have beenobtained in a variety of systems through studies of protein kinases, we have chosen to focus on this family of molecules. Several members of the protein kinase family have been shown to contribute to mammary carcinogenesis both in humans and in rodent model systems. Moreover, over-expression of genes encoding certain protein kinases, such as HER2/Neu, has been shown to provide prognostic information relevant to clinical outcome and response to therapy. As such, further studies of the function of protein kinases in the breast may reveal significant features of the relationship between development and carcinogenesis in this organ, as well provide insight into how the decision to proliferate or differentiate is made in mammary epithelial cells. We have identified two novel protein kinases, Hunk and Punc, that are: differentially regulated in the mammary gland during pregnancy; expressed in spatially restricted subsets of epithelial cells during specific stages of pregnancy; and differentially expressed in murine breast cancers induced by the Neu and c-myc oncogenes. Our studies suggest that Hunk and Punc may play a role in normal mammary development, may represent markers for biologically important subsets of epithelial cells in the breast, and may contribute to the process of mammary carcinogenesis. We hypothesize that Hunk and Punc play critical roles in mammary development by mediating pregnancy-induced changes in proliferation and differentiation. These hypotheses will be tested by using a tetracycline-inducible system to conditionally express Hunk and Punc in nontransformed mammary epithelial cells in vitro and in transgenic animals in vivo. Mice bearing targeted deletions of Hunk and Punc will be used to determine the impact of loss of function mutations in these kinases on mammary development, specifically withrespect to changes in cellular proliferation, apoptosis, and programs of differentiation that occur during pregnancy. In this application we propose to investigate the role played by two novel protein kinases in normal mammary development as a step toward understanding the relationship between development and carcinogenesis in the breast. Beyond the further elucidation of this important relationship, we believe that these studies will yield an improved understanding of the regulation of mammary epithelialproliferation and differentiation during pregnancy, and will thereby help illuminate a stage of mammary development that contributes to the determination of breast cancer susceptibility.

Grant #	Last Year Active	Organization	Project Description	Relevant Cancer Site	Area of Research	Abstract
CA85242	2000	University of Pittsburgh at Pittsburgh	Optimal Reference Exam for Mammographic Interpretations	Breast Cancer	Early Detection, Diagnosis and Prognosis/Technology and/or Marker Evaluation with respect to Fundamental Parameters of Method	As many women have annual mammograms as part of screening for breast cancer, many of them have multiple older mammograms available to compare with the current mammogram. In a high volume, rapid screening program, it is not practical for a radiologist to compare all of the prior mammograms to the current examination. We are not aware of any comprehensive study that investigates the diagnostic performance as a function of the reference examination nor is a there an age dependent optimal reference (e.g. 2 year prior for women age 55 and over or I year prior for women under 55 years of age). In addition to the possibility of an age dependent optimal reference, there may be a difference in an age dependent optimal reference in women who take hormone replacement therapy and those who do not. In this study, we will ask seven radiologists to diagnose 180 cases under four different reading modes similar to a screening environment. Except the first mode that does not include a comparison to the prior examinations, all other three modes will include a prior mammogram for comparison with the current examination. The time interval between two examinations will be either one, two, or three years. Hence, using an R0C-type methodology, we will investigate how these environments affect (or not) reader-performance, and we hope to find an effective and efficient reading mode for the majority of patients. Alternatively, we may find that different modes are optimal for different patients (e.g., for different age groups).
CA85913	2000	Fred Hutchinson Cancer Research Center	HRT Use and Risk of Lobular and Ductal Breast Cancer	Breast Cancer	Biology/Cancer-Related Biology	DESCRIPTION (Adapted from the Applicant's Abstract): Incidence rates of invasive lobular breast carcinomas (ILBC) have increased steadily in the United States since 1977, whereas the trend of increasing incidence of ductal breast cancer has plateaued since 1987. This rise in lobular tumors has occurred specifically among women over age 50. The use of combined estrogen-progestin hormone replacement therapy (CHRT) has also risen steadily over this time period, and recent analyses from two case-control investigations suggest that postmenopausal women who use CHRT may have an increased risk of ILBC, whereas there is no relationship of CHRT to ductal cancer. Few epidemiologic studies have assessed how known or suspected risk factors for breast cancer differ across different histologic types, but such investigations are important because there are likely to be multiple pathways leading to the development and progression of breast cancer of different histologic types. The primary objectives of this proposed study are to confirm recent preliminary findings that CHRT is associated with lobular breast cancer in a large population-based study, to assess this relationship in greater detail, and to explore mechanisms for this association. We propose to conduct a case-control study of 900 women aged 55-79 who have been diagnosed with breast cancer (450 lobular, 450 ductal) and 450 population-based controls who reside in the three county Seattle-Puget Sound metropolitan area of western Washington. The specific questions to be addressed are: (1) Is the use of CHRT associated with an increase in the incidence of invasive lobular breast cancer in women aged 55-79. (2) Is the use of CHRT associated with an increase in the incidence of invasive ductal breast cancer in women aged 55-79? (3) Do the duration, patterns and/or recency of CHRT use influence he size of the association? (4) Is the use of CHRT associated with alteration in the histologic characteristics, tumor cell proliferation, or expression of steroid hormone receptors, oncogenes, and cell cycle and cell death regulator proteins of lobular and ductal breast cancers?
NR05084	2000	University of Washington	Breast Cancer Survivors: Exercise and Raloxifene	Uncoded	Early Detection, Diagnosis and Prognosis/Resources and Infrastructure Related to Detection, Diagnosis, or Prognosis	It is estimated that 178,799 women will be diagnosed with breast cancer in 1998. While breast cancer has become more treatable, the long-term treatment-related side effects have a significant negative effect on morbidity and non-cancer related risk of mortality. The increasingly common use of adjuvant chemotherapy for breast cancer has led to a rise in long-term treatment- related side effects including osteoporosis, early menopause, increased risk for cardiovascular disease, and declines in quality of life. Osteoporosis is a major public health problem and a common finding in breast cancer survivors. Nationally, 20 million women are estimated to be at risk for osteoporosis, with 1.3 million sustaining osteoporotic fractures. Four factors place breast cancer survivors at high risk for muscle, bone and cardiovascular complications: inactivity, menopause (especially premature menopause), chemotherapy and catabolic steroids. This innovative study will use a randomized placebo-controlled design to test the effects of (a) exercise and (b) raloxifene in postmenopausal breast cancer survivors (N=240) between 3 months and one year after completing chemotherapy on: one resorption, formation and density (serum osteocalcin and bone specific AST, urine n-telopeptide, DEXA scan); multidimensional quality of life (SF-36, 12-minute walk, muscle strength, fatigue, menopausal vasomotor symptoms positive and negative affect, and Trail Making); and lipid profile (serum lipid levels). Subjects in the exercise intervention will follow a supervised home-based exercise program and asked to exercise 5 days/week. Exercise dose and adherence will be monitored with Caltrac accelerometers, exercise logs, regularly scheduled follow-up phone calls and supervised exercise sessions, and results on 12-minute walks and 1-repetition maximum tests. Subjects in the ralosifene and placebo control groups will be asked to take the medication (60mg/day) or placebo as prescribed. Subjects in the exercise+raloxifene group will be asked to take the medication and follow the exercise program. All subjects will be instructed to take a daily calcium supplement (1000mg/day). Subjects will be followed for 2 years. All measures will be re-evaluated at 3- month intervals except the DEXA scans, which will be obtained at 12-month intervals. Results of this study may reduce the morbidity, mortality and health care costs of these common, long- term complications that confront breast cancer survivors.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

(NICHD)

National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development (NICHD) seeks to assure that every individual is born healthy, is born wanted, and has the opportunity to fulfill his or her potential for a healthy and productive life unhampered by disease or disability. To pursue this mission, the NICHD conducts and supports laboratory, clinical, and epidemiological research on the reproductive, neurobiological, developmental, and behavioral processes that determine and maintain the health of children, adults, families, and populations. Central to this mission, the NICHD portfolio encompasses substantial women's health research that spans reproductive function and infertility disorders, contraceptive development and evaluation, HIV and AIDS, pregnancy and childbirth, menopause, prevention of certain chronic conditions, and disability issues.

The NICHD's research in the reproductive sciences includes studies on reproductive function from birth through menopause, as well as reproductive diseases or conditions that adversely affect women's health. Research related to menopause spans the basic physiological mechanisms that trigger menopause to demographic and behavioral models of reproductive aging.

For example, one of the projects that the Institute supports examines the physiological development of the human ovary from birth to menopause. Researchers are examining factors that may determine how many follicles a woman will have as she ages and how this contributes to how late she can bear children. In another project, researchers are investigating how a carbohydrate, galactose, may shorten a woman's reproductive lifespan lead to premature menopause. The findings from these studies may enable researchers to develop novel treatments to help women delay reaching menopause early. This is especially important now that an increasing number of women are waiting to have children later in life.

The Institute also supports research that examines how treatments that ameliorate menopausal symptoms affect pre-existing reproductive disorders. For instance, researchers are investigating how much hormone replacement therapy (HRT) may contribute to increasing fibroid growth. In addition, scientists are using animal models to evaluate the effects of HRT after the ovaries are removed. The findings from these studies will help scientists determine the risks and benefits of HRT and, in turn, help women choose the best treatments to meet their specific health needs.

To better understand why African American women have a greater prevalence of reproductive disorders than women in the white population, the Institute is supporting research that addresses this health disparity issue. For instance, researchers are using certain biological markers to follow ovarian aging to clarify which factors make women most susceptible to ovarian hormone deficiencies and bone density loss. These findings may provide the basis for researchers to develop treatments that help reduce the high prevalence of reproductive disorders in African American women.

While researchers are determining the normal stages involved in the aging of ovaries, other NIH-supported researchers are developing statistical models that weave together the various biological aspects of transitioning into menopause. Such statistical models will help researchers understand how changes in the physiological processes relate to the physical symptoms women experience when transitioning into menopause. For instance, researchers are trying to better understand how steroids

and hormone-related molecules help to regulate the menstrual cycle to determine how reproductive aging starts. The findings will help researchers to identify what causes the different patterns in the way women experience the transition to menopause and provide a foundation for future studies to examine the health consequences of these varied patterns of reproductive aging.

NICHD Menopause Related Grants

Grant Number	Title	Principle Investigator	Institution
5F32HD07994 03	OVARIAN FUNCTION IN RURAL BANGLADESHI FEMALES	HOLMAN, DARRYL J	PENNSYLVANIA STATE
5P30HD28138 08	AGING AND THE HYPOTHALAMIC-PITUITARY REPRODUCTIVE AXIS	HALL, JANET E	MASSACHUSETTS GENERAL HOSPITAL
5P30HD28138 08	DEPRESSION AND HYPOGONADISM	HARLOW, BERNARD L	MASSACHUSETTS GENERAL HOSPITAL
5P30HD28263 10	BIODEMOGRAPHIC MODELS OF REPRODUCTIVE AGING	WOOD, JAMES W	PENNSYLVANIA STATE
5R01HD34159 05	BIODEMOGRAPHIC MODELS OF REPRODUCTIVE AGING	WEINSTEIN, MAXINE A	GEORGETOWN UNIVERSITY
5R01HD34482 04	HORMONE REPLACEMENT AND RISK OF UTERINE FIBROID GROWTH	KJERULFF, KRISTEN H	UNIVERSITY OF MARYLAND BALT PROF SCHOOL
5R01HD38673 02	MODEL FOR PELVIC FLOOR DISORDERS	CLARK, AMANDA L	OREGON HEALTH SCIENCES UNIVERSITY
5R01HD38679 02	MECHANISMS OF INCONTINENCE FOLLOWING VAGINAL DISTENSION	DAMASER, MARGOT S	LOYOLA UNIVERSITY MEDICAL CENTER
5R03HD36518 03	OVARIAN TOXICITY OF GALACTOSE	HUGHES, CLAUDE L, JR	CEDARS-SINAI MEDICAL CENTER
5R29HD37360 03	AGING OF THE NORMAL HUMAN OVARY FROM BIRTH TO MENOPAUSE	KLEIN, NANCY A	UNIVERSITY OF WASHINGTON
1R41HD36579 01	BIODEGRADABLE IMPLANT FOR ESTROGEN REPLACEMENT THERAPY	MONKHOUSE, DONALD	THERICS, INC.
5U01AG12505 05	POPULATION STUDY OF MENOPAUSE IN AFRICAN AMERICAN WOMEN	POWELL, LYNDA H	RUSH-PRESBYTERIAN-ST LUKES MEDICAL CTR
5U01NR04061 05	PERIMENOPAUSE, BONE AND ARTHRITIS IN AFRICAN AMERICANS	SOWERS, MARY F	UNIVERSITY OF MICHIGAN AT ANN ARBOR

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

(NIDDK)

National Institute of Diabetes and Digestive and Kidney Diseases

The following are examples of completed or ongoing research relevant to menopause supported by the National Institute of Diabetes and Digestive and Kidney Diseases.

Diabetes

Diabetes Prevention Program (DPP): The Diabetes Prevention Program was the first major clinical trial in the U.S. to show that moderate changes in diet and exercise can delay and possibly prevent type 2 diabetes in a diverse population of overweight people with impaired glucose tolerance (a condition in which blood glucose levels are higher than normal but not yet diabetic). The DPP enrolled more than 3,800 participants--67 percent of whom are women and 45 percent of whom are from minority groups. The DPP found that modest weight loss—5 to 7 percent of body weight—and increased physical activity, such as brisk walking for 30 minutes per day, can cut a person's risk of developing type 2 diabetes by more than half. The DPP also found that the oral diabetes drug metformin (Glucophage®) reduces type 2 diabetes risk, although not as effectively as lifestyle changes. The lifestyle intervention worked equally well in men and women and in all the racial/ethnic groups represented in the study. ORWH is providing support for a number of ancillary studies in the DPP. One example is assessing the correlation between glucose intolerance, insulin resistance and androgenic profile, as well as the various treatment modalities on pre- and perimenopausal women of different ethnic backgrounds. Findings from the DPP will help advance understanding of the factors that lead to the development of type 2 diabetes and have provided evidence that it can be prevented.

Biochemical and Genetic Markers of Type 2 Diabetes Risk: Diabetes mellitus is a major and increasing public health problem, affecting 16 million Americans--of whom 15 million have type 2 diabetes. This study will utilize the Nurses' Health Study, a large prospective cohort including over 120,000 female nurses currently aged 54 to 79. A novel hypothesis implicates inflammation and endothelial dysfunction in the pathogenesis of type 2 diabetes. Researchers plan to study the role of several novel and promising biomarkers of inflammation and endothelial dysfunction as predictors of risk of type 2 diabetes. In addition, the pathogenic roles of specific genetic markers associated with inflammation and endothelial dysfunction will be studied. Elucidation of interrelationships between these biomarkers and development of type 2 diabetes may suggest new treatment and/or prevention strategies. Several unique features of the Nurses' Health Study, including its prospective design, large size, long duration, high follow-up rates (exceeding 90 percent over 20 years), availability of stored blood specimens, and cost-efficiency, make this database an unparalleled resource in the etiologic study of type 2 diabetes in women.

Complications of Diabetes

Cardiac Risk Factors in Hispanics with Type 2 Diabetes: Cardiovascular disease (CVD) is the most common cause of both morbidity and mortality in people with type 2 diabetes. Diabetic women have be shown to have a comparable incidence of CVD mortality with diabetic men, regardless of age. Apparently, the "protective" effects of estrogen observed in non-diabetic women are not observed in diabetic women. Hispanics have shown an increasing incidence rate of CVD that is nearly all accounted for by diabetes. Hispanic women with poorly controlled type 2 diabetes have been found to have a more atherogenic lipid profile than Hispanic diabetic and non-diabetic men. If close control of

blood glucose restores the gender differences in CVD risk factors, this study could have great implications regarding the treatment of diabetic women.

Obesity

Look AHEAD (Action for Health in Diabetes): This multicenter, randomized clinical trial will examine the effects of a lifestyle intervention program designed to promote weight loss through reduced calorie intake and regular exercise in approximately 5,000 volunteers. Look AHEAD will examine how the lifestyle intervention affects heart attack, stroke, and cardiovascular-related death in people with type 2 diabetes--the disease most affected by overweight and obesity. The study will recruit individuals between 45 and 75 years of age with type 2 diabetes, who are classified as overweight or obese. Equal numbers of men and women will be enrolled and approximately 33 percent of the participants will come from ethnic minority groups.

Weight Control in Peri- and Early Postmenopausal Women: Obesity is a preventable condition that contributes significantly to morbidity and mortality. A women's risk for obesity, as well as cardiovascular disease and osteoporosis increase dramatically with menopause due to hormonal and lifestyle changes. Furthermore, many perimenopausal women are already at risk for obesity based on current overweight or obesity, former obesity, or a family history of obesity. In light of evidence that reversal of obesity generally is difficult and unsuccessful over the long-term, a preventive approach that emphasizes modest lifestyle modifications may be superior in promoting long-term behavioral changes and weight control with advancing age. This study will assess the effectiveness of a modest lifestyle intervention program on preventing gains in body weight, whole body adipose tissue mass, and abdominal adipose tissue during a two-year period in perimenopausal and early postmenopausal women who are at risk for obesity. The results of this project may provide valuable information regarding lifestyle programs that may assist women in controlling body weight at a time when weight gain is common.

Menopause Effect on Obesity, Energy Balance and Insulin: Menopause has been associated with changes in body composition and increased cardiovascular risk factors in Caucasian women, although less information is available on the effects of menopause in African American women. Changing levels of reproductive hormones are central to the physiological changes at menopause and, since these hormones have been related to body fat distribution, it is likely that they play a role in body fat-related changes at this time of life. The overall goal of this study is to assess the influence of menopause on body composition and fat distribution, and to determine mechanisms that may influence body fat changes, in a cohort of Caucasian and African American women. This research will test four general hypotheses. First, menopause increases both total and visceral abdominal fat. Second, that changes in body composition and body weight at menopause are mediated, at least in part by changes in 24-hour energy expenditure, physical activity and/or food intake. Third, menopause results in decreased insulin sensitivity that may predispose certain women to develop diabetes later in life. These changes in insulin action may be connected to changing adiposity or may be independently related to hormonal changes. Finally, there may be a differential responsiveness to menopausal changes in African American women, who tend to have differences in adiposity, insulin sensitivity, and reproductive hormone levels premenopausally compared to Caucasian women. Since health statistics for African American women are significantly worse than for the U.S. Caucasian population, understanding the effects of menopause on risk factors in African American women is of great public health significance.

Profile-Based, Internet-Linked, Obesity Prevention Trial: The increasing prevalence of obesity and its co-morbidities and the limited success of previous weight loss/maintenance interventions argues the need for new approaches to prevent obesity. Peri-menopausal women are at high-risk to develop overweight and obesity. During this time, physiological and behavioral factors contribute to changes in energy expenditure which promote energy surfeit and progressive gain of total and abdominal fat, often exacerbated by the loss of lean tissue. This trial will develop and test an innovative individualized weight loss/maintenance program for overweight peri-menopausal women, driven by frequent assessment of the subject's biopsychosocial profiles--allowing timely intervention response to individual needs. The intervention is delivered through extensive use of new communication technologies--primarily an Internet-CD-ROM package--which have been largely unexplored in behavioral and biological research. The Internet technology represents a potentially low cost and effective means for providing the continuous education, encouragement and social support to foster sustained behavior change and weight loss/maintenance.

Endocrinology

Pathogenesis and Therapy of Autoimmune Thyroid Disease: Autoimmune thyroid disease (AITD) affects at least six percent of all women in their lifetime, and more than ten percent of older women. This research program aims to understand the causes of human autoimmune thyroid disease, the mechanisms involved in controlling the immune response, and if possible, to develop preventive or therapeutic measures based on the immunology of the disease.

Menopause, IDDM and Autoimmunity--The FAD Study: The Familial Autoimmune and Diabetes (FAD) Study has shown that the prevalence of Hashimoto's thyroiditis is higher among adult women with type 1 diabetes than their non-diabetic sisters or mothers. These findings suggest that one's ability to maintain immunological self-tolerance may be lost prematurely among women with type 1 diabetes. This may also reflect one of the many chronic complications that occur at an early age among affected individuals. It is expected that other indicators of advanced biological age may be common among women with type 1 diabetes. Self-report data from the FAD study supports this hypothesis. The mean age at menopause for women with type 1 diabetes was nearly ten years younger than that for their non-diabetic sisters. This appears to be the first formal report of an association between type 1 diabetes and early menopause in the literature. Moreover, the public health importance of these data, which must be confirmed is enormous. Given the high incidence of cardiovascular disease and other complications known to be associated with long-term diabetes, an early natural menopause is likely to exacerbate the risk of myocardial infarction among young women with type 1 diabetes. This study will validate the extremely important finding that menopause occurs at a significantly younger age among type 1 diabetic women when compared to non-diabetic women. It will also evaluate the potential differences in menstrual bleeding patterns, menopausal symptomatology and the determinants of age at menopause among type 1 diabetic compared to non-diabetic women. In addition, the study will evaluate the effect of the menopause transition on major cardiovascular disease risk factors and risk of autoimmune thyroid disease among type 1 diabetic compared to non-diabetic women.

Bone Loss and Osteoporosis

Dietary Calcium and Bone Loss in Premenopausal Women: Osteoporosis affects approximately 15 to 20 million women in the U.S. Prevention of this disease would be more beneficial and economical than treating the disease once bone loss and fractures have occurred. Dietary calcium has been implicated in the regulation of bone turnover and inadequate calcium intake has been postulated to be

important in the development of osteoporosis in women. Studies have reported that increased calcium intake in premenopausal women is associated with increased bone mass and results in greater bone mass as these women enter menopause. This study will determine if calcium supplementation in women who have attained peak bone mass can prevent the subsequent bone loss that occurs prior to menopause.

Can Parathyroid Hormone Reverse Glucocorticoid-Induced Osteoporosis: Glucocorticoid-induced bone loss is the most common cause of drug-related osteoporosis. It is especially severe in patients over 50 years of age and in those postmenopausal women. The important anti-inflammatory and immunosuppressive properties of this class of drugs have prompted their extensive use; however, side effects are many and bone loss resulting in vertebral fractures is the most incapacitating. Attempts to treat glucocorticoid-induced osteoporosis include calcium, vitamin D3 replacement, and anti-resorptive agents such as bisphosphonates, calcitonin and estrogen. All of these therapies seem to slow further bone loss but none have been able to increase bone mass. Recently, studies in humans and animals have shown that parathyroid hormone (PTH) administered intermittently in relatively low doses stimulates bone formation. This study will determine if treatment with a synthetic human parathyroid hormone fragment will reverse glucocorticoid-induced osteoporosis in patients with rheumatic disease on chronic low dose glucocorticoid treatment.

Urinary Tract Health

Health Behavior, Menopause, and Urinary Tract Infection: Urinary tract infections (UTI) affect approximately three percent of all women aged 45 to 65 each year. Although single infections are generally self-limiting and easy to treat, some women suffer from chronic recurring infections. The impact of recurring infections on quality of life can be substantial. Hormonal changes with aging and associated impact on the vaginal flora and peri-urethral environment may explain at least part of the increased risk of UTI with age. This study will examine how menopause and associated use of supplemental estrogen modifies the relationships between health behavior, bacterial virulence factors and the risk of UTI among Caucasian and non-Caucasian women aged 40 to 65. If this study identifies risk factors which, if modified, could prevent even a small proportion of the over 800,000 UTI that occur annually in this age group, this study may make a significant contribution to women's health.

Risk Factors for Urinary Tract Infections in Post-Menopausal Women: Urinary tract infections (UTI) are one of the most common infections in women. Research on the epidemiology and etiology of UTI has concentrated on two groups of women--the young and healthy and the elderly and debilitated. In younger women, general debility, voiding problems, diabetes, and possibly estrogen deficiency are risk factors. Little is known about risk factors for UTI in women soon after menopause, even though there are approximately 56 million women aged 50 to 75. This project will prospectively determine the incidence of acute UTI and assess risk factors for this problem in postmenopausal women. The primary aims of the study are to learn the relative effects of diabetes, postmenopausal estrogens, urine incontinence or increased post-void residual urine, and sexual activity on the risk of UTI. There are also plans to determine whether changes in the vaginal bacterial flora predispose to UTI in this age group and how risk factors, such as diabetes and estrogen therapy affect the vaginal flora.

Urinary Incontinence--Reproductive/Hormonal Risk Factors: Childbirth, hysterectomy and hormone use have all been implicated as risk factors for urinary incontinence (UI) based on previous epidemiologic studies. Physiologic studies suggest that pelvic nerve and muscle damage during

parturition may be associated with an increased risk for UI in the post-partum period. While UI is relatively uncommon after the immediate post-partum period, its prevalence increases with age. However, no study has examined the relationship between specific reproductive events and UI in later life. This epidemiologic study will assemble a retrospective cohort of long-term female members of a large health maintenance organization to determine the association between specific childbirth events, hysterectomy, hormone use and UI in later life. This study may also provide important descriptive information on UI by type, age group, ethnicity, severity, and age of onset. Because UI is a common condition with substantial economic and quality of life impact, identifying modifiable risk factors for UI would have a potentially large impact on public health.

Behavior and Stimulation Therapy for Stress Incontinence: Urinary incontinence in the elderly is a major problem with significant medical, psychological and social consequences. Previous research on stress incontinence has demonstrated that behavioral interventions and electrical stimulation are effective for many individuals. However, it is clear that no one method has been 100 percent effective and may have disadvantages. The broad objective of this study is to improve the treatment of stress incontinence by improving the efficacy of individual treatment modalities, by combining treatments that may have additive effects and by studying further the mechanisms by which therapies reduce incontinence.

End Stage Renal Disease

Role of Ovarian Senescence in End Stage Renal Disease: National end stage renal disease (ESRD) registries have reveled that the progression of many renal diseases is more aggressive in men than it is in age-matched pre-menopausal women. The progression to renal disease as well as the risk for cardiovascular disease, bone loss and cognitive function is also much less in post-menopausal women on estrogen replacement therapy (ERT) compared to those without ERT. Thus, hormonal responses within the kidney may be involved in the risk factors associated with ESRD. There is accumulating evidence that estrogen has a regulatory influence on the renin angiotensin system. These studies may provide further insight into the mechanisms underlying the well-documented sexual dimorphism observed in the progression of renal pathology and in the increased incidence of ESRD with ovarian senescence.

Sexual Health

Female Sexual Arousal: Clitoral and Vaginal Physiology: Sexual arousal disorder may be chronic, progressive, age-related and adversely affect quality of life and interpersonal relationships. In particular, sexual arousal disorder has been linked to age, menopause, hysterectomy, and vascular risk factors. Overall clinical management of affected patients has been primarily psychologically and hormonally-based. There has been limited research attention to the physiologically or medically-based conditions which adversely affect the female sexual arousal response. Recently, increasing numbers of affected women are utilizing "off-label" oral vasoactive agents for treatment of diminished genital swelling/lubrication responses in the absence of physiologic and clinical trial data, suggesting a need for improved female sexual health care management. The overall goal of this study is to define the physiological mechanisms underlying the arousal component of the female sexual response. These results of these studies should provide new and useful information concerning physiological and pathophysiological mechanisms in female sexual arousal and to potentially improve diagnostic and treatment strategies for women suffering from sexual dysfunction.

NATIONAL EYE INSTITUTE

(NEI)

National Eye Institute

Menopause Related Grants

Grant Number	Title	Principle Investigator	Institution
5K24EY00395-02	PATIENT ORIENTED OPHTHALMIC RESEARCH AND MENTORSHIP	SCHEIN, OLIVER D	JOHNS HOPKINS UNIVERSITY
2R01EY03306-22	MUCINS OF THE OCULAR SURFACE	GIPSON, ILENE K	SCHEPENS EYE RESEARCH INSTITUTE
5R01EY05612-14	GENDER, SEX STEROIDS AND DRY EYE SYNDROMES	SULLIVAN, DAVID A	SCHEPENS EYE RESEARCH INSTITUTE
2R01EY05640-16A2	THE ROLE OF RETINOIDS IN LACRIMAL GLAND FUNCTION	UBELS, JOHN L	CALVIN COLLEGE
5R01EY05801-16	BASAL/LATERAL--ENDOMEMBRANE TRAFFIC IN LACRIMAL ACINI	MIRCHEFF, AUSTIN K	UNIVERSITY OF SOUTHERN CALIFORNIA
5R01EY05912-12	OCULAR IMMUNOPATHOLOGY IN AUTOIMMUNE MODELS	JABS, DOUGLAS A	JOHNS HOPKINS UNIVERSITY
5R01EY06177-16	MECHANISM OF LACRIMAL GLAND SECRETION	DARTT, DARLENE A	CHEPENS EYE RESEARCH INSTITUTE
5R01EY06769-13	CORNEAL EPITHELIAL STEM CELLS	LAVKER, ROBERT M	UNIVERSITY OF PENNSYLVANIA
2R01EY07380-11A2	INTERACTIVE CELLULAR CONTROLS LACRIMAL GLAND FUNCTIONAL	MENERAY, MICHELE A	LOUISIANA ST U HLTH SCIS CTR NEW ORLEANS
5R01EY07391-13	CONTROL OF EYELIDS IN NORMAL AND PATHOLOGICAL STATES	EVINGER, LESLIE C	STATE UNIVERSITY NEW YORK STONY BROOK
3R01EY09747-08S1	OCULAR TEAR SECRETION BY THE LACRIMAL GLAND	LAURIE, GORDON W	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
5R01EY10056-07	CORNEAL EPITHELIAL CELL GROWTH FACTORS AND RECEPTORS	WILSON, STEVEN E	UNIVERSITY OF WASHINGTON
5R01EY10151-09	TEAR FUNCTION IN BLEPHARITIS AND DRY EYE	MATHERS, WILLIAM D	OREGON HEALTH AND SCIENCE UNIVERSITY
5R01EY10550-07	PROLACTIN AS A LACRIMAL GLAND IMMUNOREGULATOR	SCHECHTER, JOEL E	UNIVERSITY OF SOUTHERN CALIFORNIA
2R01EY11386-	MICROTUBULE-BASED	HAMM-ALVAREZ,	UNIVERSITY OF

Grant Number	Title	Principle Investigator	Institution
04	TRANSPORT IN LACRIMAL GLAND FUNCTION	SARAH F	SOUTHERN CALIFORNIA
5R01EY11631-04	SOLUTE AND FLUID TRANSPORT ACROSS THE CONJUNCTIVA	CANDIA, OSCAR A	MOUNT SINAI SCHOOL OF MEDICINE OF NYU
7R01EY11915-04	PATHOGENESIS OF CONJUNCTIVAL SQUAMOUS METAPLASIA	PFLUGFELDER, STEPHEN C	BAYLOR COLLEGE OF MEDICINE
5R01EY12383-02	STIMULUS/SECRETION COUPLING IN DISEASED LACRIMAL GLAND	ZOUKHRI, DRISS	SCHEPENS EYE RESEARCH INSTITUTE
5R01EY12416-02	REGULATION OF PROTEIN SYNTHESIS IN THE LACRIMAL GLAND	BEUERMAN, ROGER W	LOUISIANA ST U HLTH SCIS CTR NEW ORLEANS
1R01EY12430-01A1	MEIBOMIAN KERATOCONJUNCTIVITIS	MCCULLEY, JAMES P	UNIVERSITY OF TEXAS SW MED CTR/DALLAS
5R01EY12526-02	CONJUCTIVAL MAST CELLS IN ALLERGIC EYE DISEASE	BARNEY, NEAL P	UNIVERSITY OF WISCONSIN MADISON
1R01EY12689-01A1	ANTI-INFLAMMATORY GENES IN AUTOIMMUNE DACRYOADENITIS	TROUSDALE, MELVIN D	DOHENY EYE INSTITUTE
5R29EY11224-05	PROTEINS IN MOLECULAR MECHANISMS OF TEAR FILM FORMATION	GLASGOW, BEN J	UNIVERSITY OF CALIFORNIA LOS ANGELES
3R37EY02580-20S2	CORNEAL PRESERVATION AND KERATOPLASTY	KAUFMAN, HERBERT E	LOUISIANA ST U HLTH SCIS CTR NEW ORLEANS
3R44EY11077-03S1	DEVICE TO AID SELF ADMINISTRATION OF EYEDROPS	FRIED, GEORGE	JF SCIENTIFIC INDUSTRIES, INC.
2R44EY12573-02	DEVELOPMENT OF A BIOPOLYMER-BASED TEAR FILM SUPPLEMENT	ELLIS, EDWARD J	VISTA SCIENTIFIC, LLC
5U10EY013018-02	CAROTENOIDS AND AGE-RELATED EYE DISEASE IN WOMEN'S HEALTH	MARES-PERLMAN, JULIE	UNIVERSITY OF WISCONSIN MADISON

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

(NIAMS)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Menopause Related Grants

Grant Number	Title	Principle Investigator	Institution
24AR45734-03	NIH OSTEOPOROSIS & RELATED BONE DISEASES RESOURCE CENTER	DAWSON-HUGHES, BESS V	NATIONAL OSTEOPOROSIS FOUNDATION
AR35582-15	OSTEOPOROTIC FRACTURES	CAULEY, JANE A	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
01AR35583-15	OSTEOPOROTIC FRACTURES (SOF)	HARRIS, EMILY L	KAISER FOUNDATION RESEARCH INSTITUTE
01AR35584-15	OSTEOPOROTIC FRACTURES	HOCHBERG, MARC C	UNIVERSITY OF MARYLAND BALT PROF SCHOOL

Grant Number	PI Name	Project Title	Institution	Abstract
AR043510	BOYCE, BRENDAN F.	STUDIES OF THE FATE OF THE OSTEOCLAST	UNIVERSITY OF ROCHESTER	Osteoclasts are required for the normal development of bone during endochondral osification and for the resorption of worn-out bone in the adult skeleton during normal bone remodeling. They also mediate the increased bone loss that occurs in association with inflammation in bone and estrogen deficiency following menopause. Recent studies indicate that expression of M-CSF and RANK (receptor activation of NF-kappaB) ligand is required for osteoclast formation and that activation of genes regulated by the transcription factors, c-fos, PU.1 and NF-kappaB is also necessary. NF-kappaB regulates the expression of the osteoclastogenic cytokines, IL-6, IL-1, and TNF whose expression is up-regulated in inflammatory bone diseases and in response to estrogen deficiency. These cytokines also prevent osteoclast apoptosis, and the increased bone resorption seen after the menopause may in part be due to prolongation of osteoclast life spans on bone surfaces. NF-kappaB has also been shown to prevent TNF- and FAS ligand-induced apoptosis of some cell types and therefore may be involved in the regulation of osteoclast life span. Thus, NF-kappaB may regulate not only the formation of osteoclasts in normal bone remodeling, but also the increased production and prolonged life spans after the menopause. However, the molecular mechanisms whereby NF-kappaB mediates these activities in osteoclasts in osteoclasts are largely unknown and are likely to involve multiple signaling pathways in osteoclasts and their precursors and osteoblasts. We propose to use a combination of in vitro and in vitro approaches to study the role of NF- kappaB in osteoclast formation, activity and survival. Our specific aims are to determine the role of NF-kappaB in 1) osteoclast formation 2) the up- regulation of osteoclastogenesis induced by cytokines and estrogen deficiency and 3) the regulation of osteoclast apoptosis Our underlying hypothesis is that NF-kappaB is required for the activation of genes encoding cytokines which are essential for 1) the progression of osteoclast precursors along a differentiation pathway to form mature osteoclasts; 2) the up-regulation of osteoclastogenesis following estrogen withdrawal; and 3) for the survival of osteoclasts by preventing them from undergoing apoptosis. Understanding the role of NF-kappaB in osteoclastogenesis and survival could lead to the development of new therapeutic agents designed specifically to inhibit bone resorption in conditions, such as postmenopausal osteoporosis, in which it is increased.
AR030692	RAMSEY-GOLDMAN, ROSALIND	EPIDEMIOLOGY OF OSREOPOROSIS IN WOMEN WITH LUPUS	NORTHEWESTERN UNIVESITY	Systemic lupus was once considered a fatal disease in young women, but patient mortality and morbidi have significantly improved in the last decade. As women with lupus approach a normal life expectancy, they are at risk for low bone mineral density (BMD). The precise frequency of low BMD in Caucasian and African-American women with SLE is unknown, although preliminary evidence has documented an increased frequency of low BMD and fractures in Caucasian women with lupus. The reasons for low BMD in lupus patients are unclear. Little is known on BMD or fractures in African-American women with lupus despite the fact that this racial group is afflicted by lupus three to four times as often as Caucasian women. Although corticosteroids may play a role, there is evidence that they may not be as important as other disease factors or alteration of traditional osteoporosis risk factor consequent to diagnosis and treatment. The overall goals of this project are to conduct both a cross-sectional study and a longitudinal study to determine the effect of lupus on low BMD and the rate of bone loss in 256 women with lupus and 256 close friend healthy controls matched for age, gender, race, and menopause status. BMD at the hip and lumbar spine and all risk factors will be measured at study entry and after two years of follow-up. Risk factors to be studied include: 1) traditional osteoporosis risk factors that may be affected by the consequences of the disease and/or its treatment (reproductive history, menstrual and menopause status, use of oral contraceptives and/or hormone replacement therapy, physical activity, and vitamin D levels); 2) disease specific risk factors (disease activity, disease severity, and renal disease); and 3) treatment related risk factors (corticosteroids and anticonvulsants). Data will be analyzed using t- tests, classification and regression trees (CART), and correlation and multiple regression analyses. This study will contribute to work done by other investigators by; examining the relationship between BMD and potentially reversible or preventable risk factors for low BMD. This information will direct the development of intervention strategies to prevent low BMD and subsequent fracture in these high risk patients.
AR002074	KARLSON, ELIZABETH W.	ANTIOXIDANTS AND FEMALE HORMONES IN THE ETIOLOGY OF RA	BRIGHAM AND WOMEN'S HOSPITAL	The candidate is an Instructor in Medicine in the Department of Medicine, Division of Rheumatology, Immunology and Allergy at the Brigham and Women's Hospital and Harvard Medical School. Her research area is the epidemiology of rheumatic diseases, and the social and biological determinants of outcome in rheumatic diseases. Dr. Matthew Liang, Director, Multipurpose Arthritis and Musculoskeletal Diseases Center (MAMDC), Professor of Medicine at Harvard Medical School and Professor of Health Policy and Management at Harvard School of Public Health, will be her sponsor and co-mentor along with Drs. Frank Speizer, Charles Hennekens, Walter Willett and Meir Stampfer from the Channing Laboratory and Division of Preventive Medicine. The research training program consists of the two studies described below, Research Seminars in the MAMDC, Channing Laboratory and Division of Preventive Medicine, courses at the Harvard School of Public Health, and close review by an Advisory Committee. The goal of the proposed studies is to define the role of dietary and hormonal risk factors in the development of rheumatoid arthritis (RA) in women. Specifically, it will test the potential protective role of antioxidants and N-3 fatty acids on the risk of RA, whether postmenopausal estrogen reduces risk and whether menopause increases risk of RA. The study utilizes information from two separate, complementary cohorts, the Nurses' Health Study, a prospective cohort of 121,700 women aged 30-55 years at baseline, followed since 1976, and the Women's Health Study, a randomized, double-blind, placebo-controlled trial of nelow-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among 39,876 female health professionals, aged 45 years and older. RA will be confirmed by a screening questionnaire regarding rheumatic symptoms and review of medical records. The study will identify potentially modifiable risk factors for primary prevention of RA.
AR045825	KIMBRO,KEVEN	TRANSGENIC OSTEOBLAST SPECIFIC ER ALPHA GENE EXPRESSION	CLARK ATLANTA UNIVERSITY	Previous investigations have shown that estrogen plays a significant role in the development and maintenance of bone in mammals. The abrupt loss of estrogen at menopause and subsequent bone loss supports this hypothesis. However, the majority of the investigations to date involve the use of a gonadal castrated rodent model in order to induce a reduced hormone state. With the development of the estrogen receptor-alpha knockout mouse, ERKO, we propose to show the direct role of estrogen receptor-alpha in bone development and maintenance. Our specific aims are to clone the promoter of an osteoblastic-specific (i.e., human osteocalcin promoter) upstream of the ER-alpha cDNA and introduce this transgene into the ERKO mouse. This proposal will investigate the basic regulation of the osteoblast specific promoter-driven estrogen receptor- alpha in various osteoblast-like cell lines by transfection and use of chloramphenical acetyltransferase, Northern, and receptor binding assays. This construct will ultimately be introduced into a C57Blk/J6 mouse by using transgenic technology. The creation of an osteoblast- specific ER-alpha expressing mouse can then be used to measure overexpression of the estrogen receptor-alpha in a wild type genetic background, enabling us to understand estrogen's role in bone development and osteoporosis. The ER-alpha osteoblast expression in an ERKO background would begin to allow us to address the role and action of the ER-alpha gene in bone homeostasis in an ER-alpha negative background.

Grant Number	PI Name	Project Title	Institution	Abstract
AR043618	BEAMER, WESLEY G.	GENETIC AND DYNAMIC ANALYSES OF PEAK BONE DENSITY	JACKSON LABORATORY	DESCRIPTION: (Adapted from investigator's abstract) Osteoporosis is a bone wasting disease that afflicts about 20 million Americans. Osteoporotic fractures occur when bone density (BD) falls below the fracture threshold, a change dependent upon the peak bone density achieved by young adulthood and the subsequent net bone loss after the menopause. Up to 70% of the variation in peak BD within is inheritable. Recognizing that it is important to identify genes responsible for peak BD, the applicants initiated studies in genetically-defined inbred strains of mice. This led to discovery of a genetic model with two inbred mouse strains, C57BL/6J and C3H/HeJ, with highly significant differences in vertebral (11%), tibial (34%), and femoral (54%) BD. By using a combination of pQCT, serum and urine biochemical assays of bone formation (BF) and bone resorption (BR), and histomorphometry, they have obtained the following preliminary data. The C3H/HeJ mice (highest BD) differed from the C57BL/6J mice in the following manners: 1) reduced medullary cavity volume and increased cortical thickness; 2) increased metaphyseal trabecular BD, indicating interstrain differences occur at the endosteum and at trabecular bone: 3) decreased serum osteocalcin, serum skeletal alkaline phosphatase, and urine crosslinks/creatinine at 2 months of age; and 4) decreased osteoclast number at both endosteal cortex and trabecular bone at 2 months of age, suggesting that at this time point, decreased BR contributed to the interstrain difference in BD. Based on this preliminary data, they have advanced two hypotheses: 1) the interstrain difference in BD is determined by a fixed number of genes that can be mapped; and 2) the interstrain difference in BD is a consequence of gene effects on endosteal/trabecular BF or endosteal/trabecular BR, or both. To test the first hypothesis, a combination of genetic crosses and molecular analytic approaches will be applied to: 1) intercross F2 progeny for quantitative trait loci analyses (QTL) with the C57BL/6J and C3H/HeJ strains, plus recombinant inbred (RI) strain analyses using the BXH RI strain set derived from C57BL/6J and C3H/HeJ progenitors; and 2) recombinant congenic (RC) strains plus backcrosses of RC strains with C57BL/6J. Correlation of BD phenotypes with segregating DNA polymorphisms will establish genetic linkage, estimate the number of genes involved with interstrain bone density differences, genetically order bone regulatory genes with major and important modifier effects, define mode of inheritance for each gene, and evaluate parent-of-origin effects on BD. To test the second hypothesis, longitudinal studies will be conducted during development of peak BD in the two inbred mouse strains, applying methodologies for BD, bone histomorphometry, and bone biochemical assays. The data obtained will be analyzed: 1) to quantitatively describe the BF and BR mechanisms that account for the increase in BD within each mouse strain; and 2) to determine the differences in BF and BR that account for the difference in peak BD between the mouse strains. Ultimately, the applicants propose to correlate the phenotypic modeling mechanisms disclosed by their dynamic studies of bone modeling with the genes mapped in the first Aim.
AR041443	WEHRLI, FELIX W.	NMR IMAGING AND STEREOLOGIC ANALYSIS OF TRABECULAR BONE	UNIVERSITY FO PENNSYLVANIA	Most osteoporotic fractures occur at skeletal locations rich in cancellous (trabecular) bone. The most widely used criterion for risk assessment is bone mineral density (BMD). However, it is well known that BMD is not a satisfactory predictor of fracture risk. Indeed, there is now compelling theoretical, experimental and clinical evidence for the role of architecture as an additional predictor of the bone's mechanical competence. During the past cycles of this project we have shown both in the laboratory and in patient studies that magnetic resonance micro-imaging (mu-MRI), in conjunction with image analysis, can predict the trabecular bone's mechanical behavior and clinical outcome, respectively. In preliminary work we have conceived a new approach toward a complete quantification of cancellous bone architecture based on three-dimensional digital topological analysis and have shown that this techniques accurately describes the conversion of trabecular plates to rods, a process well known to occur during aging and, in particular, in osteoporosis. Paralleling these developments we have made significant progress in data acquisition, processing and analysis, which improved both sensitivity and precision of mu-MRI to the extent that longitudinal studies are now feasible. During the next phase of the project we propose (i) to further develop and evaluate digital topological analysis and additional structural analysis tools; (ii) to determine the precision of the mu-MRI-derived topological and scale parameters in specimens and representative patients; (iii) to assess the sensitivity of the method to detect linearchitectural changes during early menopause in a pilot project involving women treated with estrogen and their controls; (iv) to compare sensitivity and precision of mu-MRI with DEXA and p-QCT. The overall hypothesis to be tested is that mu-MRI-based cancellous bone structural analysis is sensitive and reproducible and capable of detecting changes in cancellous bone architecture as they occur over time, either as a result of normal changes or in response to treatment. The long-term goal of the work proposed is to establish "virtual bone biopsy," analogous to physical bone biopsy, by three-dimensional architectural analysis of mu-MRI data collected in vivo, as a means to follow patients longitudinally, either as a method for assessing osteoporosis risk or for evaluating treatment efficacy.
AR045233	TURNER, RUSSELL T.	ESTROGEN METABOLITES EFFECTS ON BONE	MAYO CLINIC ROCHESTER	A serious obstacle to the rational design of innovative approaches for preventing and/or treating osteoporosis is the idiopathic nature of postmenopausal bone loss. Menopause is the most important risk factor for osteoporosis. However, not all postmenopausal women develop osteoporotic fractures indicating that cessation of the menstrual cycle is insufficient to fully account for the disorder. Our working hypothesis is that the denovo production and metabolism of estrogens are among the most important factors influencing the rate of postmenopausal bone loss. Estrone (E1) and its metabolites, 16alpha-Hydroxyl estrone ((16alpha-OHE1) and 2-hydroxyesterone (2-OHE1), are the most abundant estrogens in postmenopausal women. 16alpha-OHE1 has been recently shown to be a negative risk factor (reduced risk) for postmenopausal bone loss, whereas 2-OHE1 has been positive risk factor (increased risk). 2-OHE1 does not have estrogenic activity in ovariectomized (OVX'd) rats. In contrast, 16alpha-OHE1 appears to be a tissue selective estrogen agonist with a profile of activity similar to the anti-breast drug tamoxifen; 16alpha-OHE1 is a much more effective estrogen agonist on bone and liver than on reproductive tissues. These observations suggest that differences in the skeletal activities on 2-OHE1 and 16-alpha-OHE1 are responsible for the observed association between bone mass and circulating levels of these metabolites in postmenopausal women. We propose to test this hypothesis in ovary intact and OVX'd rats. The specific aims are to determine the dose response effects of 2-OHE1 and 16alpha-OHE1 on the expression of immediate response genes in bone and other estrogen target tissues; and establish the long-term effects of the estrone metabolites on bone architecture, turnover and strength. The proposed research will characterize the probably cellular mechanisms of action. The results of these studies are likely to be relevant to women because of the similarity between postmenopausal bone loss and OVX-induced bone loss in rats, as well as the previous success the rat model has enjoyed for predicting the response of the human skeleton to estrogen agonists and markers to predict the rate of postmenopausal bone loss; 2) manipulation of estrone metabolism by changes in diet or by pharmacological intervention may be a valuable tool for reducing bone loss; and 3) analogs of 16alpha-OHE1 may be useful for prevention and treatment of postmenopausal osteoporosis.
AR092237	RECKER, ROBERT M.	HORMONE REPLACEMENT THERAPY WITH ALENDRONATE IN POST MEN	CREIGHTON UNIVERSITY	The purpose of this contract is to conduct a randomized, double-blind, controlled trial of a combination of low-dose, continuous hormone replacement (o.d mg/day conjugated equine estrogens, +2.5 mg/day medroxyrpogesterone) with alendronate (10mg/day). The two drugs will each be tested alone and in combination in estrogen deprived, osteopenic, postmenopausal women over 60 years of age. Each of the three groups will enroll 72 participants and follow them for three years. Calcium and Vitamin D supplements will be given to all participants throughout the study. The hypothesis that will be tested is that the combined therapy shows a greater bone effect than either drug given alone. The primary outcome measures will be spine bone mineral density, total hip bone mineral density, and total body bone mineral content.

Grant Number	PI Name	Project Title	Institution	Abstract
AR039559	LOHMAN, TIMOTHY G.	BONE ESTROGEN STRENGTH TRAINING	UNIVERSITY OF ARIZONA	Osteoporosis is an increasingly important public health concern for women, contributing to over 1.3 million fractures per year. With the increase in the elderly population, a three fold increase in hip fractures, the most costly fracture, has been projected, with costs for treating all osteoporotic fractures increasing from $13.8 Billion in 1995 to $60 Billion by the year 2020. While the effects of dietary and hormonal interventions on BMD are being investigated in the Women's Health Initiative, the effects of exercise, a potentially effective stimulus for slowing and possibly reversing bone loss is not assessed. In this renewal we propose to complete intervention and assessments for a large partially randomized clinical trial evaluating the effect of one year of exercise on total body and regional BMD in two population (hormone replacement therapy (HRT) versus no HRT) of postmenopausal women. We also propose to add measurements of bone biomarkers and endocrine factors to our existing data base to investigate correlates of BMD underlying the potential response to exercise and to extend follow-up for an additional two years to assess the long-term effects in women who continue exercising versus women who do not exercise. We hypothesize that exercise will significantly increase BMD and that exercise plus HRT is a more effective stimulus than exercise or HRT alone. Thus, exercise will be an efficacious alternative to risk reduction of osteoporosis. The study is unique in its design (random assignment) population (HRT versus no HRT), sample size (N=279), and the comprehensive assessment of physiological, nutritional, and morphological correlates of BMD. Duplicate (one week apart) blood collections and DXA scans are done at each measurement period (baseline 6 and 12 months) to improve precision to follow changes in biomarkers, hormones, soft tissue composition, and axial and appendicular BMD. Extensive dietary intake data are collected using diet records and food frequency questionnaires. The exercise program (progressive resistance exercise and weight bearing aerobic exercise) is designed to provide high strain magnitudes, rates and a diverse distribution, all thought to be osteogenic stimuli. Exercise compliance is carefully monitored through extensive workout records of exercise frequency, intensity duration and type, and by measuring muscle strength gains. Study adherence for the initial four cohorts (of 6 cohorts) was 92 percent. Thus, as we show, we have excellent power to assess short-term and long- term exercise effects. Because of the paucity of information regarding long term effects of exercise, and because of the increased emphasis called for in the scientific community for evaluating the long-term efficacy of exercise for osteoporosis prevention, this comprehensive one year clinical trial and two year follow-up will make an important contribution to a valid prescription of exercise for the prevention of osteoporosis in two populations (HRT vs no HRT) of postmenopausal women
AR044655	BECK, THOMAS J.	Structural Analysis Of DEXA Scans: Osteoporosis Studies	JOHNS HOPKINS UNIVERSITY	This abstract is not available.
AR042540	BUYON, JILL P.	SAFETY OF ESTROGEN IN LUPUS ERYTHEMATOSUS-NAT'L ASSESS'	HOSPITAL FOR JOINT DISEASES ORTHO INST	The current proposal addresses the effect of exogenous female hormones on disease activity and severity in women with systemic lupus erythematosus (SLE). Oral contraceptives (OCs) and estrogen replacement therapy (ERT) are generally not prescribed due to the widely-held view that they can activate SLE. This practice is based on the greater incidence of SLE in women than in men, biologic abnormalities of estrogen metabolism, murine models of lupus, several anecdotes of patients having disease flares while receiving exogenous hormones, and a single retrospective study in patients with pre-existing renal disease. In contrast, recent retrospective studies suggest that the rate of flare is not significantly increased in patients taking OCs or ERT. The pre- existing data are insufficient to warrant the dismissal of a potentially important birth control option in a disease which predominantly affects women in their reproductive years and whose fertility is not altered by the disease. Moreover, the use of OCs to preserve fertility in patients taking cyclophosphamide, and the use of estrogens to prevent coronary artery disease and postmenopausal and steroid-induced osteoporosis are timely considerations. In Specific Aim 1 we will attempt to define, in a randomized double-blind placebo-controlled trial, the effect of OCs containing low dose synthetic estrogens and progestins on disease activity in women with SLE. Since the research hypothesis is that OCs do not increase the risk of flares, the study has been designed to be able to detect minimal increases in the rate of flares in patients taking OCs. Patients with \pard softlineinactive, stable or moderate disease requiring less than 0.5 mg prednisone per kg of bodyweight per day will be enrolled over a 2-year period and randomized to receive triphasic ethinylestradiol/ norethindrone or placebo for 12 months. In Specific Aim 2, we will) examine, in a randomized double-blind placebo-controlled trial, the effect of hormonal replacement with conjugated estrogens and cyclic low- dose medroxyprogesterone acetate on disease activity in postmenopausal women with SLE. Patients will be enrolled over 3 years and receive hormones for 1 year. This multicenter study represents a first-time clinical research collaboration between 5 major rheumatology centers: Hospital for Joint Diseases/Bellevue Hospital/New York University, Hospital for Special Surgery/Cornell University Medical, St. Luke's/Roosevelt Hospital Center, The Johns Hopkins Medical Center, and UCLA School of Medicine/LA County Harbor Medical Center. Patients will be recruited from the clinics and private practices which include over 4,000 women with SLE, most belonging to minority groups. The proposal embraces the cooperative efforts of rheumatology, reproductive endocrinology, epidemiology, and biostatistics, to initiate needed prospective controlled studies. Such approaches have already changed long-held beliefs about the risk of lupus flares during pregnancy.
AR002113	DAVIS, JOHN C.	ANDROGEN AS ADJUNCT THERAPY IN RHEUMATOID ARTHRITIS	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	Rheumatoid arthritis (RA) is a chronic, debilitating multisystem disease affecting nearly two million persons in the United States alone. The incidence of RA in men under the age of forty-five is less than that reported in women, however the incidence approaches that of women in older age groups of men. This increased incidence in males coincides with decreasing levels of sex hormones. A hypogonadic condition characterized by low serum testosterone has been previously described in male RA patients compared with age-matched controls with osteoarthritis, ankylosing spondylitis and healthy controls. Patients with RA have significant disability with decreased function over time. Androgens have the potential to increase nitrogen retention, lean body mass, strength, and body weight which could slow the decline in function. Patients with RA also have both local and systemic forms of osteoporosis. There is evidence that androgens may stimulate the proliferation and differentiation of osteoblasts and osteoblast-like cells in vitro which may help reduce the rate of bone loss in RA. Previous studies in both animal models and humans seem to suggest that androgen administration may be beneficial in a number of autoimmune diseases including RA. In this study, we will examine the role of transdermal testosterone versus placebo in male patients with RA over a two-year period. Specifically, we will examine (1) the effect of testosterone on lean body mass and muscle strength with the use of whole body dual xray absorptiometry (DXA) scan and muscle strength testing, (2) the effect of testosterone on bone mineral density by DXA scan of the spine and hip, and (3) the effect of testosterone on disease specific measures of quality of life with validated instruments for quality of life. Additionally, measure of disease activity and side effects will also be assessed. The results of this study will (1) help to define the role of androgen administration and its effects on function through assessment of muscle mass and strength, (2) explore the potential benefits of testosterone therapy on bone mineral density in patients with both localized and systemic forms of osteoporosis, (3) define changes in quality of life in patients with RA treated with androgen, and (4) help to define the potential role of androgen therapy in other systemic illnesses where muscle wasting has a profound impact on quality of life (e.g. both inflammatory and non-inflammatory muscle disease). In addition, this K-23 grant will provide opportunity for further career development through mentorship provided by an committee with multiple areas of expertise and formal education in the areas of clinical research design and conduct, outcome assessment development and analysis, and clinical trial analysis.
AR042739	GIGER, MARYELLEN L.	Computerized Radiographic Analysis of Bone Structure	UNIVERSITY OF CHICAGO	This abstract is not available.

Grant Number	PI Name	Project Title	Institution	Abstract
AR008574	LEDER, BENJAMIN Z.	DIFFERENTIAL EFFECTS OF ANDROGENS AND ESTROGENS ON BONE	MASSACHUSETTS GENERAL HOSPITAL	Osteoporosis affects over 20 million Americans and leads to considerable morbidity and mortality. Although osteoporosis is more common in women, largely due to postmenopausal estrogen deficiency, it also develops in men. Hypogonadism is a leading risk factor for osteoporosis in men. Still, it is unknown if androgen deficiency, estrogen deficiency, or both lead to hypogonadal bone loss in men. In the proposed study, 75 normal men (ages 20-45) will be randomly assigned to one of three groups (n=25 per group). Group 1 will receive a GnRH agonist (Zoladex, 3.6 mg q 4 wks) for 12 weeks, thereby suppressing endogenous gonadal steroids to pre-pubertal levels. Group 2 will receive the GnRH agonist plus testosterone replacement (Androderm, 5 mg/day), thereby normalizing circulating testosterone and estradiol levels. Group 3 will receive the GnRH agonist plus Androderm plus an aromatase inhibitor (Femara, 2.5 mg/day), thereby normalizing testosterone but causing a selective estrogen deficiency. Bone turnover markers (bone specific alkaline phosphatase, osteocalcin, urinary N-telopeptide, and urinary deoxypyridinoline) and calcium regulatory hormones will be measured every 4 weeks. Bone turnover will increase in Group 1 and should remain unchanged in Group 2. If androgens alone are sufficient to maintain normal bone turnover in adult males, bone turnover should not increase in Group 3. If, however, estrogens are also required to maintain normal bone turnover in men, bone turnover should increase in Group 3.
AR039191	LINDSAY, ROBERT	SPECIALIZED CENTER OF RESEARCH IN OSTEOPOROSIS	HELEN HAYES HOSPITAL	Osteoporosis is recognized has a major public health problem in the USA today, with the likelihood of increased societal impact as "baby boomers" age. Therapeutic options are currently limited to "anti-resorptive" therapies which reduce bone turnover. Therapeutic options are currently limited to "anti-resorptive" therapies which reduce bone turnover, stabilize bone mass and reduce but not eliminate fracture risk, in part because many treated individuals are left with a bone mass that remains less than optimal. Thus, there is a clear need for agents that stimulate new bone formation. Our Specialized Center of Research has assembled a panoply of basic and clinical scientists to focus on this issue. Over the past 9 years we have investigated interactions of parathyroid hormone and sex steroids in the development and treatment of osteoporosis. Our cohesive and integrated approach has generated a significant base of knowledge, culminating in the demonstration that PTH (superimposed on standard HRT) not only increases bone mass but may also reduce vertebral fracture risk. In our current application, in four inter-related and integrated projects, we will examine aspects of PTH action at both basic and clinical levels. In Project 1 we will use novel techniques to isolate functional human osteoclasts and transgenic murine models to examine the mechanisms underlying osteoclast differentiation and death. In Project 2 the ovariectomized rat model will be used to evaluate morphological, biochemical, and mechanical responses to PTH, comparing a model of primary hyperparathyroidism (continuous PTH infusion) with intermittent PTH administration, in both estrogen replete and depleted states. The next project uses the paradigm of endogenous primary hyperparathyroidism in post-menopausal women to characterize the effects of chronically increased PTH, and its reduction (after parathyroidectomy) on skeletal homeostasis. The last project focusses on the mechanism underlying the initial period of new bone formation that occurs in the early months of PTH therapy, as well as the effects of withdrawal of treatment. Each of these projects relies heavily on the support of "Core" units,: Administration/Statistics; Biochemistry; Histomorphometry; and Bone Mass Measurement, with integration of all Projects and Cores with regard to protocols, investigators and data interpretation.
AR041398	KIEL, DOUGLAS P.	RISK FACTORS FOR AGED RELATED BONE LOSS	HEBREW REHABILITATION CENTER FOR AGED	DESCRIPTION: (Adapted from Investigator's Abstract) Osteoporosis and related fractures represent major public health problems that will only increase in importance as the population ages. Several studies have now convincingly demonstrated that aging-related bone loss continues, and may even accelerate, in extreme old age. A better understanding of the factors that may be unique to bone loss in old age may help to refine the types of interventions to preserve bone mass in old age. The present application is a competing continuation proposal from the Framingham osteoporosis study group to examine in detail several risk factors for bone loss in old age using three related cohorts, the original Framingham cohort, The Framingham Offspring cohort and a new Framingham minority cohort. The Original Framingham cohort has been the subject of two previous exams that included measurement of bone density. The Framingham Offspring Cohort was recruited from among the children, and their spouses, of members of the original cohort starting in 1971; 3570 are expected to participate in this osteoporosis study. The Minority cohort is currently being recruited and will consist of 300 subjects (34% black and 66% Hispanic). The proposed studies will extend and expand upon the research group s previous investigations of more traditional risk factors for bone loss by taking advantage of developments in nutritional assessment, as well as findings from cellular and molecular biology of bone, which offer an opportunity to examine risk factors for bone loss that have been less well studied. The primary aim (1) of the proposed studies is to examine the effect of dietary factors on bone health, in particular the effect on bone density and bone loss of consumption choices among common food groups, and the effect on bone loss of specific nutrients that have not been well-studied with regard to bone, including magnesium, potassium, vitamin C, sodium, and vitamin K. The dietary studies will be performed using longitudinal data on bone density from the original Framingham cohort, and using cross-sectional bone density data in the Offspring and Minority Cohorts. Dietary data, in the form of food frequency questionnaires in all three cohorts, and 3 day food records in the Offspring Cohort, have already been collected at previous examinations. For this aim, follow-up for bone loss in the Original Framingham Cohort will be extended from 4-5 years to 8 years by adding an assessment of bone density at a planned future Framingham biennial examination (Exam 24). A special call back visit will be required to obtain bone density in all of the approximately 3,600 members of the Offspring Cohort. Both dietary data and bone density are already being measured in an ongoing examination of the Minority Cohort. There are also several other Aims of the study, as follow: (2) to examine the cross-sectional association of IGF-1 and IGF-BP4 with bone density in a subset of 100 men and 100 women in the Framingham Offspring cohort using blood specimens obtained 5 years prior to the measurement of bone density; (3) to examine the cross-sectional association with bone density of two new measures of weight-bearing physical activity, a validated questionnaire and an automated weight-bearing activity monitor, in subsets of 200 men and 200 women in each of the Original and Offspring Cohorts; physical activity will also be examined in relation to a new measurement of QUS of the heel in this subset from the Original cohort; the physical activity measures will be obtained in a special callback or regular visit in the Offspring Cohort and at Exam 24 in the original cohort; and (4) to compare measures of quantitative ultrasound (QUS) of the calcaneus between members of the Original Cohort who attend Exam 24 and those who are unable to attend the exam to determine if bone loss may be underestimated by studying subjects who attend clinic examinations. QUS will be assessed with a new dry system device in all those in the original cohort who attend Exam 24 as well as those who receive the standard Framingham home visit.

Grant Number	PI Name	Project Title	Institution	Abstract
AR044661	BOUXSEIN, MARY L.	LOW COST METHODS TO ASSESS OSTEOPOROTIC FRACTURE RISK	BETH ISRAEL DEACONESS MEDICAL CENTER	Osteoporosis is a common condition that presently affects more than 25 million persons in the US, contributing to over 1.5 million fractures annually. The economic and social impact of these fractures on health care delivery and on the elderly population are staggering. Furthermore, if current trends continue, the number of fractures and associated costs are projected to double or triple in the next 30 years due to the aging of our population. Early identification, through widespread screening programs, and intervention in those persons at high risk may improve the success of fracture prevention strategies. The most commonly used technique for assessing fracture risk, dual-energy x-ray absorptiometry (DXA), though proven effective as a predictor of future fracture risk, may not be the ideal screening tool due to the relatively high capital investment required, the need for specialized operator training, and limited portability. Recently, alternatives to DXA have been developed. We propose studies designed to further our basic understanding and to evaluate the potential usefulness of two of these alternative methods: image analysis of conventional radiographs and quantitative ultrasound (QUS). In the first two aims we will evaluate a diagnostic technique based on image processing of conventional forearm radiographs. In this technique, a bone index representing the character of the projected trabecular pattern is computed from standard radiographs. We will compare this bone index to the strength of cadaveric femurs and thoracolumbar vertebrae, and assess its ability to predict hip fracture risk in case-control study of women with an acute hip fracture and similarly-aged women who have not suffered a fracture. In our final aim, we will examine the capabilities of QUS. It has been proposed that QUS measures aspects of bone "quality", such as trabecular architecture, material properties, or accumulated microdamage, that are independent of bone density. However there have been few studies relating QUS measurements on intact feet (rather than excised bone specimens) to aspects of bone quality. We will use human cadaveric specimens to characterize the relationship between QUS measurements of on intact feet and trabecular bone morphology, mechanical properties, and microdamage. The significance of the proposed work is that is will provide new information regarding the potential usefulness of two technologies that may be capable of widespread osteoporosis testing and assessment of fracture risk. This information is important, as early identification of those at risk for fracture represents the most promising approach for effective fracture prevention.
AR042358	FEDARKO, NEAL S.	ESTROGEN RECEPTOR STRUCTURE/FUNCTION IN AGING BONE	JOHNS HOPKINS UNIVERSITY	The long term objective of the proposed research is to determine the biological function and molecular mechanism of recombinant human insulin like growth factor-I (rhIGF-I). Insulin like growth factor-I (IGF-I) is a polypeptide that has the potential to modulate osteoblast cell function. The proposed studies are an outgrowth of clinical studies designed to determine the effects of rhIGF-I and estrogen on skeletal turnover in postmenopausal women. In order to understand the mechanisms involved in IGF-I action on bone, the Principal Investigator proposes to study the effects of rhIGF-I on the extracellular matrix metabolism of human osteoblasts in vitro. Specifically, to measure the effect of IGF-I on mRNA expression and protein levels of extracellular matrix components, bone cell IGF-I response as a function of the age of the patient and mineralized state of the matrix, stability and competency of the matrix as a scaffolding for mineralization, and the influence of growth hormone (GH), estrogen, and parathyroid hormone (PTH) on bone cell response to IGF-I. The steady-state levels of bone matrix protein and mRNA for type I collagen, the proteoglycans biglycan and decorin, osteonectin and alkaline phosphatase will be analyzed to determine the effect of IGF-I on the composition of the bone cell matrix. Protein and mRNA levels will be determined by techniques developed by the Principal Investigator or utilized in prior studies of human osteoblast extracellular matrix metabolism. The effect of the temporal sequence of bone cell development in culture, either a pre-mineral or a mineralizing extracellular matrix, on IGF-I responsiveness will be assessed by comparing steady-state matrix composition for young adult (10-18 years) and adult (over 50 years) human trabecular bone cell cultures. The stability of the extracellular matrix will be assessed by radiolabeling and pulse-chase analysis of these specific bone matrix components. The effect of IGF-I on the competency of the matrix as a site for mineral deposition will be assessed by determining both the in vitro time frame of mineralization and by analyzing the mineral content and protein (including osteocalcin) of the extracellular matrix. The endocrine modulation of human bone cell responsiveness to IGF-I will be investigated by characterizing the effect of GH, estrogen, and PTH on matrix content (steady-state radiolabeling), stability (pulse-chase radiolabeling), and competency for mineralization. The approach of assaying extracellular matrix composition and stability and mineralization in response to IGF-I treatment and systemic factor modulation will define an integrated pattern of in vitro bone protein and proteoglycan metabolism and bone mineralization.
AR043391	MUNGER, RONALD G.	NUTRITION, GENES AND HIP FRACTURE RISK IN UTAH	UTAH STATE UNIVERSITY	DESCRIPTION: (Adapted from Investigator's Abstract) The investigators propose a population-based case-control study of the role of novel nutritional and genetic factors in the etiology of hip fractures in Utah residents, ages 50 years or older. They will recruit 950 women and 950 men with incident hip fractures from a random sample of all hip fractures among Utah residents during 1997-00 and an equal number of sex- and age-matched controls. The following hypotheses will be tested. 1. Low intake of protein is associated with an increased risk of hip fracture; analyses will be extended to include source and quality of protein intake and lysine intake. Covariates in analyses will include intakes of total energy, lipid, carbohydrate, calcium, and vitamin D. 2. Allelic variants of candidate gene markers associated with osteoporosis increase the risk of hip fracture. They will study genes that are involved in bone formation and remodeling, including COL1A1 and COL1A2, the genes that encode the chains of type 1 procollagen, the vitamin D receptor, osteocalcin, osteonectin, and osteopontin. The goal is to evaluate the risk of hip fracture attributable to these candidate genes within the context of a representative human population. 3. The candidate genes and nutrients mentioned above interact, additively or multiplicatively, to increase the risk of hip fracture. Individuals with high-risk alleles for osteoporosis may be more susceptible to nutritional and other environmental causes of hip fracture. A pilot study of hip fractures among Native Americans (50 cases, 100 controls) will develop appropriate methods, including dietary assessment. Fractures among Native Americans are understudied and this minority group includes subgroups with considerable variation in bone density, dietary habits, lifestyle habits, environmental exposures, and genetic traits. The investigators state that the multidisciplinary approach proposed may lead to effective public health interventions to reduce the burden of hip fractures.

Grant Number	PI Name	Project Title	Institution	Abstract
AR046859	PREVRHAL, SVEN	MEASUREMENT OF THICKNESS/DENSITY OF THE PROXIMAL FEMUR	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	DESCRIPTION (Taken from the application): Hip fracture is one of the most severe implication of Osteoporosis, a disease affecting millions of elderly people world-wide. The clinically established method to predict a person's hip fracture risk, bone densitometry, cannot separately measure the status of trabecular and cortical bone but only reports overall bone density. There is evidence that both compartments individually contribute to bone strength but are differently affected by aging or osteoporotic changes and therapeutic regimens. This research effort will approach the following questions: Can the density and the thickness of cortical bone in the proximal femur be measured accurately with volumetric Quantitative Computed Tomography (vQCT)? Does the knowledge of these parameters aid in predicting mechanical integrity in addition to standard bone densitometry? To what extent is the technique applicable in vivo? To assess the accuracy of vQCT, a comparison to Micro-CT is planned. Micro-CT is a Computed Tomography technique on microscopic level (the spatial resolution is 25 mm for the instrument being used) and has recently been extended to scan whole proximal femora. It can therefore be used as a gold standard to evaluate vQCT. Out of a total of 25 excised cadaveric proximal femora from elderly women who did not have diseases known to affect bone, 5 will be scanned with vQCT and Micro-CT. The analysis tools, which will comprise segmentation of the cortical wall and local measurement of cortical bone mineral density and thickness, will be applied to both data sets. The other 20 specimens will be subjected to vQCT, standard bone densitometry and mechanical testing. During the latter, bone elasticity and ultimate failure load will be recorded. The gathered data will allow to estimate the relative contribution of the cortical thickness and density to mechanical integrity and to locate the most sensitive regions of the cortex. The question of whether a vQCT scan of cortical bone can add information to standard bone densitometry can also be answered. The third part of the study will focus on clinical feasibility of vQCT of cortical bone. Its specific aim is reducing the radiation exposure by limiting the CT scan volume and decreasing the amount of radiation used. By analyzing the impact of the consequential increase of image noise and loss of spatial resolution on the measurability of cortical density and thickness optimal CT imaging parameters will be derived.
AR008633	WANDSTRAT, AMY E.	IDENTIFICATION OF SLE1B AND ITS ROLE IN AUTOIMMUNITY	UNIVERSITY OF TEXAS SW MED CTR/DALLAS	Systemic lupus erythematosus (SLE) is a complex genetic disorder and occurs 8-9 times more frequently in women than men with variable penetrance. In the lupus-prone mouse strain, NZM 2410, four regions have been identified on chromosomes 1, 4, 7, and 17. We are interested in identifying the gene(s) known to be responsible for the autoimmune response seen in SLE. Isolated in congenic mouse strains against a C57BL/6 background, the chromosome 1 region, Sle1, has been associated with either loss of tolerance to chromatin or increased immune response leading to splenomegaly and production of autoantibodies. The region of murine chromosome 1 that Sle1 maps to is syntenic to human chromosome 1 where a locus for lupus susceptibility has been linked (29- 33). Therefore, identification of the mouse gene may also help in identifying the human gene. We have been able to further narrow the Sle1 region using congenic meiotic recombinants and have found that there are three genes in the Sle1 region, Sle1a, Sle1b, and Sle1c that confer autoantibody production. Our studies have revealed that Sle1b is the strongest of the three loci regarding antichromatin IgG production. We have a sequence-ready BAC contig of the region and will use both BAC sequencing and cDNA direct selection to identify candidate genes for Sle1b. Candidate genes will then be analyzed for proper expression and the ability to reproduce the phenotype in a B6 mouse knockout. As Sle1b may be important in focusing the autoimmune response to selected targets, identification of the gene will be important in understanding how the autoimmune cascade is initiated.

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

(NCCAM)

National Center for Complementary and Alternative Medicine

Menopause Related Grants

GRANT NO.	TITLE	PRINCIPLE INVESTIGATOR	INSTITUTE
AT00090	CENTER FOR CAM RESEARCH IN AGING	KRONENBERG, FREDI	COLUMBIA UNIVERSITY
	MACROBIOTIC DIET AND FLAX SEED EFFECTS ON ESTROGENS, PHYTOESTROGENS &	KUSHI, LAWRENCE	
	DIETARY PHYTOESTROGENS AND BONE METABOLISM	BILEZIKIAN, JOHN	
	EFFECTS OF BLACK COHOSH ON MENOPAUSAL HOT FLASHES	KRONENBERG, FREDI	
	PLANT ESTROGENS: BENEFICIAL OR HARMFUL FOR BREAST CANCER	LUPU, RUTH	
AT00155	BOTANICAL DIETARY SUPPLEMENTS FOR WOMEN'S HEALTH	FARNSWORTH, NORMAN	UNIVERSITY OF ILLINOIS
	STANDARDIZATION OF BOTANICAL DIETARY SUPPLEMENTS	FARNSWORTH, NORMAN	
	ESTROGENIC AGENTS: IN VITRO AND IN VIVO EVALUATION	BOLTON, JUDY L.	
	IN VITRO STUDIES OF METABOLISM, ABSORPTION AND TOXICITY	VAN BREEMAN, RICHARD	
	CLINICAL EVALUATION OF BOTANICAL DIETARY SUPPLEMENTS	DERMAN, RICHARD J.	

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

(NIAAA)

National Institute on Alcohol Abuse and Alcoholism

Menopause Related Grants

Grant No.	*Title*	*Principle Investigator*	*Site*	*Abstract*
R01AA010234-05S1	Alcohol and Osteoporosis: An animal Model	Sampson, Herschel	Texas A&M	National health care cost for osteoporotic women is estimated to be 5 billion dollars annually and nearly a third of the elderly female population is affected. Alcohol consumption has been known to be significant contributing factor to osteoporosis and bone loss since the work of Saville in 1965. Most studies have been conducted on patients admitted for alcohol rehabilitation and are of different, ages, sexes, and lengths of drinking history and except for very short term projects, are very difficult to properly control. Some have stopped drinking for various periods of time prior to the project, others frequently have various stages of liver disease, and controls included persons with unknown alcohol intake: all leading to conflicting results and demonstrating a need for an animal model system in which to study these effects in a more controlled environment. Prior studies of the effect of alcohol on bone have fairly clearly demonstrated the induction of an osteopenia which appears similar to postmenopausal osteoporosis but possibly develops by a different mechanism. This proposal proposes to use a rat model for a series of rigorously controlled histomorphometry studies of the effects of alcohol consumption on bone and on mineral metabolism and more specifically on the development and severity of postmenopausal osteopenia. Specific objectives are to determine the life-long consequence of ethanol consumption on bone-growth in the young, maintenance in middle age, and bone loss rate in the elderly and to determine the consequence of long-term ethanol consumption on the severity and the rate of formation of ovariectomy in the rat model.
R01AA011130-04	Gender, Moderate Ethanol Intake and Bone Metabolism	Perry, Horace	St. Louis Univ	Bone loss and the resulting osteopenia contribute significantly to the increasing incidence of all kinds of fractures with age. Such fractures not only are associated with an immediate increase in morbidity and mortality, but have long term effects on mobility and independence. The long-term goal of this proposal is to study the effect is of moderate alcohol intake on bone metabolism in men and women in order to diminish the risk of bone loss and fracture which has been associated with alcohol intake. This study will evaluate alcohol intake in non-alcohol dependent individuals. The protocol will study alcohol intake and parameters of mineral metabolism including parathyroid hormone (PTH) collagen breakdown products (dipyrolidinium crosslinks) (DPC), osteoblast activity (osteocalcin) and vitamin D concentrations. The protocol will measure alcohol intake and evaluated longitudinally and their effect on BMD in men and women assessed. It will take seasonal variations of these parameters into account. Finally, the protocol will examine the effect of alcohol intake on changes in femoral and lumbar BMD in men and women. We expect that the initial BMD in men who drink moderately will be less than in those who drink minimally. In women, however, we expect greater BMD in those who drink moderately compared to those who drink minimally. This difference in the effects of alcohol on men and women will be mirrored by similar changes in gonadal steroids. These will be decreased in men who drink moderately, but increased in women who drink moderately.
AA011172	Tivis, Laura J.	Alcohol, ERT and Cognition in Menopausal Women	University of Oklahoma Hlth Sciences Ctr.	Applicants Abstract: A large proportion of postmenopausal women are at least moderate consumers of alcohol and exogenous estrogen (or lack of) on their cognitive functioning and psychological characteristics. Our first two aims are to determine whether drinking or use of estrogen replacement therapy (ERT) independently affect cognition in postmenopausal women. The third aim is to determine whether or not there are interactive effects of alcohol and ERT and if so, to determine the nature of their influence on cognitive processes. We also propose to investigate whether or not use of progestin replacement therapy (PRT) affects cognitive functioning. Four groups of postmenopausal women will be recruited; teetotalers, light moderate, and moderate heavy drinkers. Within each of the alcohol-drinking groups, 54 will ERT, 54 will be non-users. To accomplish aim 6 the teetotalers group will contain 54 non-users and 108 ERT users (54 ERT/no PRT and 54 ERT/PRT users). Alcohol use patterns are assessed. A battery of tests that measures specific neurocognitive processes will be used. Dependent variables will include accuracy, response times, and error type. Blood levels of estradiol and estrone will be measured and also used as dependent variables. Questionnaires pertaining to psychosocial characteristics will be administered. Psychosocial measures include demographic characteristics, employment history, satisfaction with family and work environments, health history, and recent life-change events. Psychosocial subscales scores will be used as dependent variables. Long-term benefits will include identification of risks and or benefits to cognition and psychosocial status associated with moderate drinking and use of ERT. These results can add to existing knowledge and provide an increased understanding of issues surrounding women's health care.
AA004610	Wilsnack, Sharon C.	Problem Drinking in Women – A 20-Year National Study	University of North Dakota	This application proposes a national survey of 1,550 women in 2001 to increase knowledge about longitudinal patterns of women's drinking. The survey will include 700 women interviewed in 1981 and 1991, 350 women first interviewed in 1991, and a new same of 500 women age 21-30 in 2001. (Subsamples of women were also interviewed in 1986 and 1996). Combining the 2001 survey with the preceding surveys will produce 20-yearcross-sectional data for all age groups, 20-year multiwave longitudinal data from women over age 40 in 2001, and 10-year longitudinal data from women age 31-40 in 2001. Specific aims of the proposed research are to evaluate (1) 20-year trends and age, period and cohort effects in women's drinking behavior; (2) predictors of 5-, 10- and 20-year age specific changes in women's drinking behavior; (3) effects on and from women's drinking trajectories across the adult life span; (4) correlates and predictors of heavier drinking among older women and among women of childbearing age; (5) effects of question formats and interview modes on women's drinking self-reports; (6) links of women's drinking patterns with disordered eating behavior and with use of prescribed psychoactive drugs; and (7) cross-national variations in women's drinking behavior and its antecedents and consequences, using data from an international collaborative project coordinated by our research group. In the 2001 survey, professional female interviewers will conduct 75- minute face-to-face interviews using many questions from previous surveys about drinking patterns, drinking-related problems, changes in work and family roles, depressive symptoms, sexual and reproductive experience and relationships with significant others. New questions will include a measure of trait impulsivity and additional questions about binge eating, estrogen replacement therapy, antidepressant use, and health problems of older age. Data analysis will include cross-tabular correlational and regression analyses; analysis of variance; cluster analysis (of drinking partnerships and drinking trajectories); structural equation modeling (for longitudinal prediction of 2001 drinking patterns); and generalized estimating equation, random regression models, latent transition analysis, and survival analysis (for comparing trends and trajectories and for predicting trajectories). The 2001 survey, combined with data from the 1981, 1986, 1991, and 1996 surveys, will yield the largest, longest-term and most detailed set of longitudinal and life-historical data yet available about U.S. women's drinking and its antecedents and consequences. Together with findings from the international collaborative gender and alcohol project, issues addressed by the proposed analyses of these data should provide a strong foundation for efforts to improve the prevention and treatment of women's problem drinking in the 21st century.

Grant No.	Title	Principle Investigator	Site	Abstract
AA000219	Berman, Marlene O.	Affective and Conative changes in Alcoholism	Boston University	This is an application for an ADAMHA Senior Scientist Award (SSA). The SSA would permit the PI (a) to devote all of her research efforts to alcoholism; (b) to expand her research and mentoring activities concerned with gender issues in alcoholism; and (c) to gain valuable experience with structural and functional neuroimaging techniques. In conjunction with 2R01 AA 07112-09, investigations are planned to examine changes in affect (emotion) and conation (intention) in abstinent alcoholics. Secondary aims of the research are to expand studies of age-related changes and gender differences in emotional and intentional functions. The importance of the research is fourfold: (1) Putative sites of alcohol-related brain damage involve separate frontal systems which are tied to different perceptual/cognitive aspects of emotional and intentional behaviors; (2) gender differences in alcohol-related neurobehavioral functions are ripe for experimental exploration; (3) the literature on whether emotional changes have reciprocal effects on perception and cognition in alcoholism is equivocal and controversial; and (4) even though affective and conative abnormalities have been clinically apparent in alcoholic groups, neuropsychological studies have focused primarily on cognitive changes unrelated to emotion and intention. In the proposed experiments we will enlist the participation of right-handed male and female research subjects ranging in age from 20 to 75 years. The experimental groups will include abstinent alcoholics with and without Korsakoff's syndrome. Patterns and levels of performances by the alcoholics will be compared to those of age-matched nonalcoholics subjects, in order to evaluate the ways in which behavioral consequences of aging and alcoholism are parallel, divergent or interactive. Additionally, patients with right-frontal or bilateral frontal lobe damage from cerebrovascular accidents will provide the necessary control comparisons for neurobehavioral changes linked directly to focal brain damage. These groups were chosen specifically to clarify frontal system contributions to deficits of Korsakoff and non-Korsakoff alcoholics. We also will be able to evaluate hypotheses about greater right-than left-hemisphere functional decline in the alcoholic and aging groups, and in women compared to men. It is expected that results of the proposed studies will show clear evidence of frontal-mediated affective and conative changes in alcoholics (most notably in the Korsakoff patients), but that these changes will not be conspicuous in aging populations uncomplicated by alcoholism. By the contrast, certain aspects of perceptual functioning will be compromised by aging whether or not a history of alcohol abuse already exists. Finally, women will display different performance patterns than men.
AA011954	Helzer, John E.	Enhancing Brief Intervention of Primary Care Physicians	University of Vermont & St. Agric College	Interactive Voice Response (IVR) is a computer-based telephone technique that allows subjects to respond to a recorded voice asking scripted questions. The caller inputs brief numeric answers using the telephone touch pad. In a series of studies, we have been using the IVR as a reporting device to examine the evolution of alcohol consumption over time and its relation to alcohol problems. In this study we propose to test IVR in a primary care practice as treatment tool to enhance physicians' brief alcohol interventions with heavy and problem drinkers. Method: after brief alcohol intervention by their physician in participating primary care clinics, consenting patients meeting our selection criteria will be randomized to one of four study groups. The first three of these are: 1) Brief intervention only: II) Brief intervention plus daily calls by the subject to the IVR: III) Brief intervention plus daily IVR calls with periodic feedback of IVR consumption data to the patient via the physician. Group IV will receive the same treatment as group III, but subjects in Group IV will receive a financial incentive to help ensure a high IVR call compliance rate. Goals: We will assess: 1) The feasibility of using IVR as an intervention in primary care patients including call compliance rates and the validity of the consumption reports, and 2) Whether an IVR with or without patient feedback enhances the effects of a brief alcohol intervention by a physician. Our long-term objective is to develop interventions specifically designed to capitalize on the unique advantages of an IVR system. The public health implications of effective, low cost interventions for heavy and problem drinking that can be accessed remotely and are applicable in primary care and HMO settings and considerable
AA011184	Gavaler, Judith S.	Alcohol and Estrogen Replacement Therapy Interactions	University of Pittsburgh	APPLICANTS ABSTRACT: By 1991 census data there are 33 million women age 50 and older, the median age at which natural menopause occurs. With the addition of surgical menopause women, there are over 40 million postmenopausal women. Estimates of the prevalence of Estrogen Replacement Therapy (ERT) use range from 12 to 33 to 45%. Estimated current moderate alcoholic beverage consumption among women age 50-60 is 59% and 37% among women over 60. Thus to 5 to 18 million are being treated with ERT, while as many as 20 million potsmenopause (PMP) women drink moderately. The number of postmenopausal who both drink and use ERT is unknown. Both ERT therapy and moderate alcohol consumption increase PMP estrogen levels; both ERT and moderate alcohol consumption significantly reduce coronary heart disease risk, the major cause of death in PMP women. There are 3 goals, of the proposed research: 1) To determine the patterns of alcohol consumption of health behaviors such as smoking, dietary habits/ nutrient intake and physical activity, and of estrogen replacement therapy (ERT) use among 1250 normal PMP volunteers of different ethnic/racial backgrounds participating in a study determinants of PMP estrogen levels. 2) To determine in normal PMP women not treated with ERT whether smoking, physical activity, nutrient intake and ethnical/racial origin influence PMP estrogen levels in addition to already identified estrogen determinants which include moderate alcohol beverage consumption, body fat mass, and ovariectomy. 3) To determine in normal PMP women related with ERT to what degree circulating levels of estrogen achieved with estrogen replacement therapy are modulated by factors which influence the production and metabolism of estrogen and other hormones in PMP women.
AA005965	Pfefferbaum, Adolf	CNS Defects-Interaction of Age and Alcoholism	SRI International	DESCRIPTION: We propose to continue using magnetic imaging (MRI), neuropsychological (NP) and event-related potential (ERP) testing to extend and refine our findings of CNS deficits associated with chronic alcoholism and aging. Our MRI studies of alcoholic man reveal volume loss in cortical gray and matter, corpus callosum, hippocampus, and mammillary bodies and enlargement of cortical sulci and lateral and third ventricles. Older alcoholic men have gray matter volume deficits particularly striking in the prefrontal cortex. Electrophysiologically, the latency of P300, a physiological index of cognitive speed, is prolonged in alcoholic men with an exaggerated prolongation in older alcoholics; further P300 latency and indices of tissue loss are significantly associated in alcoholics. Neuropsychologically, alcoholic men show deficits in executive abilities, short-term memory, fluency and visospatial abilities and especially severe deficits in balance. Our longitudinal studies demonstrate recovery of gray matter volume with abstinence and further reduction of white matter volume with continued drinking. For the competitive renewal, we propose the following studies: Study 1: fMRI experiments of localized brain activation during performance of auditory and visual working memory tasks. This study is designed to determine whether alcoholics show a pattern of cortical activation during working memory that is different from that observed in controls, and whether underlying structural deficits influence the pattern of fMRI activation. Study 2: Visual ERP and NP experiments of the interhemispheric transfer time designed to assess the functional significance of corpus colossal thinning. Study 3: Continuation of our ongoing longitudinal study of alcoholic and control women. This study is designed to identify cross sectional patterns of sparing and loss, their interaction with age and their comparability to findings in alcoholic men. Cross-sectional findings will be examined longitudinally to determine their interaction with alcohol consumption and the normal course of aging and to assess the extent to which deficits normalize with sobriety or are exacerbated with continued drinking. Study 4: A new longitudinal study in a new sample of older alcoholic men and women and their controls in order to extend with refined anatomical and new functional measures earlier findings.

NATIONAL INSTITUTE OF NURSING RESEARCH

(NINR)

National Institute of Nursing Research

Menopause Related Grants

Grant Number	Title	Principle Investigator	Institution
NR004205	WOMEN-CENTERED GROUNDED THEORY OF MENOPAUSE	DICKSON, GERI	RUTGERS, STATE UNIVERSITYOF NEW JERSEY , NEWARK
NR004259	BIOBEHAVIORAL HEALTH IN DIVERSE MIDLIFE WOMEN	LEE, KATHRYN	UNIVERSITY OF CALIFORNIA SAN FRANCISCO
NR005084	BREAST CANCER SURVIVORS: EXERCISE AND RALOXIFENE	SCHWARTZ, ANNA	
NR004141	MENOPAUSE TRANSITION-BIOBEHAVIORAL MODELS OF SYMPTOMS	WOODS, NANCY	UNIVERSITY OF WASHINGTON
NR000132	DECISION MAKING REGARDING HORMONE REPLACEMENT THERAPY	PADONU, GEORGIA	MICHIGAN STATE UNIVERSITY
NR004799	WOMEN IN TRANSITION: THE CRUCIAL YEARS BEFORE MENOPAUSE	WURZBURG, GERARDINE	STATE OF THE ART, INC.
NR004946	EXERCISE AND PERIMENOPAUSAL SYMPTOMS: A RANDOMIZED TRIAL	LI, SULING	LOYOLA UNIVERSITY OF CHICAGO
NR005281	HEART DISEASE IN WOMEN: ESTROGEN EFFECTS ON HEMODYNAMICS	SHERWOOD, ANDREW	DUKE UNIVERSITY
NR004061	THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION-MICHIGAN	SOWERS, MARYFRAN	UNIVERSITY OF MICHIGAN AT ANN ARBOR
NR005261	VENLAFAXINE FOR HOT FLASHES FOLLOWING BREAST CANCER	CARPENTER, JANET	VANDERBILT UNIVERSITY
NR001118	NURSING STUDY OF SLEEP AND FIBOMYALGIA IN MIDLIFE WOMEN	LANDIS, CAROL	UNIVERSITY OF WASHINGTON
NR007564	EFFECT OF HORMONE THERAPY AND RALOXIFENE ON SERUM LIPIDS	RODDY, SHIRLEY	UNIVERSITY OF NEBRASKA MEDICAL CENTER
NR005281	HEART DISEASE IN WOMEN: ESTROGEN EFFECTS ON HEMODYNAMICS	SHERWOOD, ANDREW	DUKE UNIVERSITY
NR005339	ESTROGEN/PLATELET INTERACTION IN CEREBRAL ISCHEMIA	KEARNEY, MARGUERITE	JOHNS HOPKINS UNIVERSITY
NR004946	EXERCISE AND PERIMENOPAUSAL SYMPTOMS: A RANDOMIZED TRIAL	LI, SULING	LOYOLA UNIVERSITY OF CHICAGO
NR005051	HORMONE REPLACEMENT THERAPY AMONG WOMEN WITH DISABILITIES	BECKER, HEATHER	UNIVERSITY OF TEXAS AUSTIN
NR005245	ESTROGEN, ANGINA, ACTIVITY AND QUALITY OF LIFE IN WOMEN	MISSIK, EUGENIA	KENT STATE UNIVERSITY @ KENT
NR000132	DECISION MAKING REGARDING HORMONE REPLACEMENT THERAPY	PADONU, GEORGIA	MICHIGAN STATE UNIVERSITY

NATIONAL INSTITUTE ON DRUG ABUSE

(NIDA)

National Institute on Drug Abuse

Menopause Related Grants

Grant Number	TITLE	PRINCIPLE INVESTIGATOR	INSTITUTION
1RO1DA0135641	NATURAL HISTORY OF MENOPAUSE IN HIV INFECTED DRUG USERS	SCHOENBAUM, ELLIE	MONTEFIORE MEDICAL CENTER (BRONX, NY)
1K12DA014040-01	INTERDISCIPLINARY RESEARCH CAREERS IN WOMEN'S HEALTH	WILSON, EMERY	UNIVERSITY OF KENTUCKY
5R01DA011324-05	OFFICE BASED METHADONE PRESCRIBING II	DRUCKER, ERNEST	MONTEFIORE MEDICAL CENTER (BRONX, NY)
5R01DA008075-07	TOBACCO CESSATION IN POSTMENOPAUSAL WOMEN	ALLEN, SHARON	UNIVERSITY OF MINNESOTA TWIN CITIES

NATIONAL INSTITUTE OF MENTAL HEALTH

(NIMH)

National Institute of Mental Health

Menopause Related Grants

Gonadal Steroid Regulation of the Biological Clock
(Horvath, Tamas-Yale University-5R01MH059847)

The long-term goal of this research is to examine the relationship between hormone levels, circadian function, and behavior, and to determine if hormones regulate the activity of the biological clock. In particular, the focus is on estrogen regulation of cells in the suprachiasmatic nucleus and lateral geniculate nucleus. The results of these experiments will reveal the mechanisms via which hormonal signals can regulate components of the biological clock. The findings will provide new insights into the etiology of discomforting symptoms of menopause, including mood swings, sleep disorders, and hot flashes, all of which are tightly coupled to the activity of the biological clock.

Cytokines and Hypothalamic-Pituitary Immune Interactions
(Wardlaw, Sharon-Columbia University Health Sciences-5R01MH055708)

This grant examines the interaction of the hypothalamic-pituitary-adrenal axis (HPA) and immune responses to stress or infection in female humans and rhesus monkeys and the influence of gonadal steroids on this response. These studies may relate to a wide range of human diseases, as cytokine interactions in the brain may be associated with neurodegeneration and immunosuppression. If sex steroids restrain these interactions, such pathology could be exacerbated when sex steroid levels fall, as in menopause. These studies will thus have direct relevance to the issue of sex steroid replacement during menopause.

Estrogen Effects on Anxiety Related Neural Systems
(Altemus, Margaret-Weill Medical College of Cornell University-5K08MH001682)

The research component of this award focuses on investigating the hypothesis that estrogen restrains fear-associated behaviors. Data indicated that reproductive hormone fluxes, like those experienced during menopause and hormone replacement therapy, have profound effects on the course of anxiety disorders and depression. The aims of this research are to study the effects of estrogen on behavioral tests of anxiety, to examine the effects of estrogen on neuroendocrine systems known to modulate fear and anxiety, and to define the anatomic sites of estrogen action on fear behaviors.

Synergy Between SSRIs and Ovarian Hormones
(Van De Kar, Louis-Loyola University Medical Center-5R01MH058448)

This grant tests the central hypothesis that estrogen acts synergistically with selective serotonin reuptake inhibitor (SSRI) treatment of depression via complementary mechanisms to desensitize serotonin 1A (5-HT1A) receptor systems and produce antidepressant effects. This synergistic action could shorten the delay in the onset of the effects of SSRIs. The proposed studies will examine the mechanisms by which estrogen modulates 5-HT1A receptor signaling. These studies will provide the scientific basis for the development of improved therapeutic regimens and novel drugs that provide faster clinical improvement in women suffering from PMS (premenstrual syndrome), depression, bulimia, and anxiety disorders.

Ovarian Steroid Regulation of Serotonin in Primates
(Bethea, Cynthia-Oregon Health & Science University-1R01MH062677)

This research project examines the manner by which estrogen and progesterone enhance serotonin neurotransmission within the primate brain. These studies are highly relevant to understanding how ovarian hormones affect neurotransmitter systems involved in the regulation of mood, cognition, and stress responsiveness. The results of these studies will be useful for understanding the distinct effects of single or combined hormone replacement therapy of post-menopausal women on central serotonergic function.

Neuroendocrine Mechanisms of Reproductive Aging
(Jennes, Lothar-University of Kentucky-5R01MH059890)

The overall goals of this research are to determine the changes that occur in the brain during reproductive aging and to reveal the underlying mechanisms that cause a gradual decline in the regularity of the estrous cycle, followed by a complete cessation of cyclicity adult female rats. The proposed studies will provide comprehensive information on the changes that occur in the regulatory input to the gonadotropin-releasing hormone neurons during reproductive aging and will determine the role estradiol plays in this process.

Mechanism for Abolishing Gonadotropin Surges by Estrogen
(Tsai, Houng-University of Kentucky-5F31MH012289)

The long-term goal of this study is to elucidate the neuroendocrine mechanisms responsible for reproductive dysfunction in aging female rats and to determine whether chronic exposure to preovulatory estradiol levels causes the loss of the luteinizing hormone surge-inducing actions of estradiol that occur in aging rats and if so, by what mechanism.

Estrogen and Cognition Over the Lifespan
(Foster, Thomas-University of Kentucky-5R01MH059891)

The long-term goal of this research is to understand the mechanisms for hippocampal-dependent memory function during aging. Estrogen treatment can delay the progression of memory loss associated with aging and Alzheimer's disease. This study tests the hypothesis that estradiol

effects on memory are due to altered calcium homeostasis. It is believed that the results of the experiments will add to our knowledge concerning the regulation of synaptic function across the lifespan and provide a basis for understanding the mechanisms for estrogen's effects on memory.

Effect of Estrogen on Hippocampal Single Unit Activity
(Tropp, Jennifer-University of Connecticut Storrs-1F31MH063551)

It has been shown that estrogen has an effect on the anatomy and activity of the hippocampus. The main objective of this project is to investigate the dynamics of the firing patterns related to normal hormone cycling as well as estrogen depletion. The effects of the absence of estrogen and estrogen replacement in the hippocampus are a major focus of this grant. The findings from this study will have important implication for understanding the processes in which memories are formed and the potential therapeutic effect of estrogen in menopausal women.

Estrogen, Hippocampal Neurogenesis, and Learning
(Gould, Elizabeth-Princeton University-5R01MH059740)

The broad objectives of this proposal are to characterize the influence of ovarian steroids and learning on the production, survival, and gene expression of hippocampal granule neurons generated in adulthood. This proposal will provide insight into the disorders of age- or disease-related cognitive decline, which can be ameliorated by ovarian steroid treatment.

Estrogen Supplementation in Late Life Schizophrenia
(Lindamer, Laurie-University of California San Diego-5K08MH001580)

The objective of this award is to aid in the development of the investigator in the field of geriatric psychiatry with a specialization in women's health issues, particularly the role of estrogen replacement therapy (ERT) in psychiatric disorders. This grant includes the execution of a project investigating the effects of estrogen augmentation of neuroleptic medication in postmenopausal women with schizophrenia, and will examine the effects of estradiol levels in general, as well as ERT in conjunction with neuroleptics, on psychopathology, cognition, and quality of life in these women.

Geropsychopharmacology—Enhancing Benefit, Reducing Risk
(Pollock, Bruce-University of Pittsburgh-5K02MH001509)

The overarching goal of this award is to improve the pharmacotherapy of late-life mental disorders through research on geriatric drug metabolism. Study Three of this grant is a pilot examination of the effects of estrogen replacement therapy (ERT) in postmenopausal women with mild to moderate depression.

Menopausal Depression: Chronobiological Basis
(Parry, Barbara-University of California San Diego-1R01MH59919)

This research project examines the effects of hormone replacement therapy on mood and circadian rhythmicity in healthy, non-depressed post-menopausal women. Subjects will be treated for 8 weeks with estradiol, estradiol plus progesterone, or placebo. Sleep/wake patterns and activity levels will be monitored after one month of treatment. At the end of the treatment period, mood, biological rhythmicity and synchrony of sleep, activity patterns, temperature, and plasma hormone secretion (melatonin and gonadotropic hormones) will be evaluated. These studies will provide important insights into the effects of hormone replacement therapy on mood and behavior and could lead to new clinical treatment guidelines for menopausal women. In addition, this research provides a basis for future studies of hormone replacement therapy on mood and circadian rhythms in depressed menopausal women.

Menopausal Transition, Mental Health, and Ethnicity
(Bromberger, Joyce-University of Pittsburgh-2R01MH059689)

This grant aims to assess whether women will be more likely to develop new or recurrent depression during the perimenopausal transition than before or after and to compare rates of new or recurrent depression across the transition for African American and Caucasian women. Studies under this grant will also determine if a history of major depression is a risk factor for depression, increased levels of perceived stress, somatic and psychological symptoms, and decreased quality of life or functioning during the menopausal transition.

ERT, Depression, and Cognition in Postmenopausal Women
(Rasgon, Natalie-University of California Los Angeles-5R29MH57423)

The pathogenesis of late-life depression and antidepressant therapeutic response may involve postmenopausal estrogen deficiency. Existing data suggest that estrogen replacement therapy (ERT) in post menopause enhances both mood and cognitive function. This research will evaluate serotonin and cognitive functions in postmenopausal depressed women compared with matched postmenopausal controls and will assess antidepressant treatment outcomes for postmenopausal depressed women. The impact of ERT on cognition will also be assessed in both depressed and control postmenopausal women. This research will provide a foundation for future investigations of the pathophysiology of reproductive-related mood disorders.

Psychobiology & Treatment of Perimenopausal Mood Disorders
(Schmidt, Peter-NIMH Intramural Research Program-1Z01MH02537)

The goals of this project are to identify the mechanisms underlying the effects of gonadal steroids on the regulation of affective states, to identify the effects of aging, menopause, and gender on the neuroregulatory actions of gonadal steroids, to determine the therapeutic utility of hormonal therapies in mood disorders occurring during midlife and perimenopause, and to identify the predictors of antidepressant response to hormone therapy in reproductive endocrine-related mood disorders.

Reproductive Endocrine Related Mood Disorders
(Rubinow, David-NIMH Intramural Research Program -1Z01MH002765)

This project studies reproductive endocrine-related mood disorders and develops endocrine models for these disorders in order to characterize the role of gonadal steroids in affective disturbance, including the effects of menopause, perimenopause, and hormone replacement therapy.

The Neurobiology of Major Depression
(Gold-NIMH Intramural Research Program -1Z01MH002659)

Depression may be a major risk factor for osteoporosis and abnormally elevated stress hormone levels may contribute to bone loss. This study will determine whether women with major depression lose bone mass at a faster rate than women without depression. This study will also determine if the drug alendronate (Fosamax) can maintain or increase bone mass in premenopausal women with major depression and osteoporosis. It is hoped that these studies will lead to the development of preventive treatments for the increased bone loss typically seen in menopausal, depressed women.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

(NINDS)

National Institute of Neurological Disorders and Stroke

Menopause Related Grants

Estrogen and Primate Brain Cells Regulating Gonadotrophin (Naftolin--5R01NS36111)
The investigator will look at the effect of the gonadotrophin delivery systems on synaptic connections and neuron activity in certain states, including ovariectomy with and without hormone replacement and in naturally occurring menopause. Three major inhibitory and three major stimulator neurotransmitter systems will be studies in this project.

Gender Differences in Stroke (Hurn--5P01NS20020)
Estrogen has been considered to be protective in coronary heart disease, but it is not clear if it is a neuroprotectant for females or males. Preliminary findings in animals indicate that females have a better outcome after stroke than males, and that ischemic events can be altered by estrogen-priming of the cerebral vasculature and the brain. The purpose of this study is to determine if there are inherent sex-linked injury mechanisms for salvaging brain tissue after an ischemic event.

Cerebral Ischemia in the Female (Hurn – 5R01NS033668-07)
Blood flow and energy metabolism in the brain is compromised during an ischemic stroke, which can lead to focused or widespread brain damage. The female hormone estrogen may aid in recovery from ischemia. The purpose of this study is to determine the extent of estrogen's effects on cerebral blood flow, energy metabolism and blood vessel reactivity during and after global ischemic stroke in both female and male subjects. Information derived from these studies should improve the current understanding of vascular function in women and address the role of estrogen as potential neuroprotective therapy for patients of either sex.

Estrogen Modulation of Brain: A-beta Metabolism in vivo (Gandy--1R01NS41017)
Evidence suggests that estrogen replacement therapy in postmenopausal women appears to reduce the risk of Alzheimer's disease (AD), or delay its onset. However, the mechanism by which estrogen exerts this neuroprotective role is unclear. The investigators will examine the role of estrogen on the release of certain peptides (A-beta) that are aggregated in the brains of AD victims. Guinea pigs, transgenic mice and cell cultures will be used to test agonist and antagonist activity on estrogen receptors and regulation and metabolism of the A-beta protein.

Neural Mechanisms of Gynecological Pain (Berkley—R01NS11892)
Vaginal sensitivity in women increases after menopause to produce vaginal hyperalgesia (VAGH), perhaps due to estrogen loss in these tissues. The grantee will test this hypothesis and other neurological bases for VAGH.

Sympathetic Nerve Remodeling in the Adult Uterus (Smith—5R01NS39570)
Published studies show that sympathetic nerve density of the virgin rat uterus fluctuates throughout the estrous cycle. Nerve density decreases during estrogen administration and mice that lack a functional estrogen receptor have uteri that are hyperinnervated. The grantees will design studies to ascertain if raising plasma estrogen will suppress uterine neurotrophic factor

production. Information gained may have direct applicability to the understanding of dysmenorrhea and autonomic dysfunction that occurs in menopause.

Epidemiology and Genetics of Parkinson's Disease (Rocca—2R01NS33978)
The investigators will sample 800 Parkinson's disease (PD) patients and 800 PD-free control subjects. Study participants will be asked about tobacco, coffee and alcohol use. Women will be assessed for estrogen replacement therapy after menopause and other reproductive and estrogen-related factors. The case-control study may confirm preliminary findings on the role of estrogen in PD.

Hormone Replacement in Menopausal Women with Epilepsy (Harden – 5R01NS038473-02)
This clinical trial will study whether standard hormone replacement therapy is safe for menopausal women with epilepsy. Seizure frequency will be monitored in postmenopausal women with epilepsy before and after treatment with either placebo or standard hormone replacement. The difference in seizure frequency between the baseline and treated phases of the placebo and hormone replacement groups will determine the safety of hormone replacement therapy for postmenopausal women with epilepsy.

Hormone Regulation of Pain Perception (Quinones-Jenab, 1U54NS041073-010001)
Women generally have lower pain thresholds and are less sensitive to morphine-like analgesics than men. The proposed studies will examine the influence of steroid hormones on pain and opioid sensitivity in a female rat model. The results may provide insight into pain management approaches for women utilizing estrogen replacement therapy after menopause.

Estrogen and Brain Control of Blood Pressure (Clark, 1U54NS041071-010001)
The incidence of cardiovascular disease in women increases dramatically following menopause, likely triggered by estrogen deprivation. Using a rat model, these studies will investigate whether estrogen deprivation results in increased blood pressure, and which estrogen-sensitive neurotransmitter systems and regions of the brain produce this cardiovascular effect. Important new information on the protective effects of estrogen on the neural regulation of blood pressure may be gained from these studies.

Estrogen Regulation in Cholinergic Systems (Sohrabji, 7R29NS036297-05)
Recent retrospective studies and small-scale clinical trials suggest that estrogen replacement therapy is beneficial for the management of Alzheimer's disease. This effect may be due to increased neurotrophic support to hormone-sensitive cholinergic neurons in the forebrain, known to be at risk in Alzheimer's disease. In this study, estrogen's ability to regulate trophic support for forebrain cholinergic circuits will be investigated as a possible means of neuroprotection during injury or disease.

Genetic and Environmental Risk Factors for Stroke (Broderick, 5R01NS036695-04)
Intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) occur in over 50,000 Americans each year and yield a combined mortality of 40-50%. This study will investigate the genetic and environmental risk factors for ICH and SAH in a racially mixed metropolitan population of 1.3 million (14% African-American). Along with many other variables included in the study, estrogen deficiency in women will be analyzed as a potential risk factor for stroke.

Womens Estrogen for Stroke Trial (WEST) (Horwitz – 5R01NS031251-08)
Results from the Womens Estrogen for Stroke Trial (WEST) (Horwitz – 5R01NS031251)
The results of an important NINDS-supported study, published in October, 2001, concluded that estrogen hormone replacement therapy does not reduce the risk of stroke or death in postmenopausal women who have already had a stroke or a transient ischemic attack (TIA), according to a report from the first randomized, controlled clinical trial of estrogen therapy for secondary prevention of cerebrovascular disease.

Previous observational studies have suggested that estrogen replacement therapy may reduce the risk of stroke and death in postmenopausal women. However, it was not clear whether the apparent benefits of estrogen among women in those studies were due to the hormone therapy or other factors. The randomized, double-blind, placebo-controlled study, called the Women's Estrogen for Stroke Trial (WEST), was designed to resolve this question. The study, led by Ralph I. Horwitz, M.D., of the Yale University School of Medicine, was funded by the National Institute of Neurological Disorders and Stroke (NINDS) and was published in the October 25, 2001, issue of *The New England Journal of Medicine*

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

(NIEHS)

National Institute of Environmental Health Sciences

Menopause Related Grants

Grant Number	Title	Principle Investigator	Institution
5R01ES007171	FEMALE REPRODUCTIVE OUTCOMES AND TCDD EXPOSURE	ESKENAZI, BRENDA	UNIVERSITY OF CALIFORNIA BERKELEY
2P42ES007384	NEUROPHYSIOLOGIC DYSFUNCTION, LEAD MOBILIZATION, AND MENOPAUSE	BERKOWITZ, GERTRUD	MOUNT SINAI SCHOOL OF MEDICINE OF CUNY
5R01ES008979	ENVIRONMENTAL EPOXIDES--MECHANISMS OF OVOTOXICITY	HOYER, PATRICIA	UNIVERSITY OF ARIZONA
5R01ES008704	LEAD EXPOSURE, GENETICS AND OSTEOPOROSIS EPIDEMIOLOGY	KORRICK, SUSAN	BRIGHAM AND WOMEN'S HOSPITAL
1Z01ES049025	CAUSES AND CONSEQUENCES OF EARLY MENOPAUSE	COOPER, G	
1Z01ES04926	MENSTRUAL & REPRODUCTIVE RISK FACTORS FOR CANCER & CHRONIC DISEASE	COOPER, G	

NATIONAL HEART, LUNG AND BLOOD INSTITUTE

(NHLBI)

National Heart, Lung, and Blood Institute

Menopause-Related Research

Because many of the diseases and conditions that fall within the NHLBI mandate (e.g., coronary disease, hypertension, congestive heart failure, chronic obstructive pulmonary disease) primarily affect older people, many postmenopausal women are being studied in the Institute's clinical research programs. This document focuses specifically on NHLBI-supported research in women that is related to reproductive hormonal status or to changes in health risks that occur as women pass through menopause.

Women's Health Initiative

The Women's Health Initiative (WHI) is a complex multicenter project examining strategies for the prevention and control of the most common causes of death, disability and impaired quality of life among postmenopausal women, including cardiovascular disease, breast and colorectal cancers, and osteoporotic fractures. Initiated in 1991 with planned completion in 2007, the WHI is conducted as a consortium effort led by the NHLBI in cooperation with the Office of Research on Women's Health, the National Cancer Institute, and the National Institute of Arthritis and Musculoskeletal Diseases. Recruitment was completed in 1998. Over 68,000 women of diverse racial, ethnic, geographic, and socioeconomic background are participating in three overlapping randomized controlled Clinical Trials (CT), and an additional 93,676 women are enrolled in a parallel Observational Study (OS). Follow-up of the entire cohort is planned through March 2005.

Clinical Trials

The CT is designed to evaluate the effect of:

1) **Low-fat eating pattern** in preventing breast and colorectal cancers (N = 48,836)
2) **Hormone replacement therapy** in preventing coronary heart disease and other cardiovascular diseases, with breast cancer as a possible adverse outcome (N = 27,347)
3) **Calcium and vitamin D supplementation** in preventing osteoporotic fractures (N = 36,282)

Women may participate in one, two, or all three trials. Overall benefit-versus-risk assessment is a central focus in each of the three CT components.

Observational Study

The OS will: 1) examine the associations of known or putative risk factors (including biomarkers) to disease status at baseline and during follow-up; 2) seek to find new risk factors using the stored biological samples and data as a resource; and 3) examine the association of change in known or putative risk factors on disease outcome.

A detailed description of the WHI is available in *Controlled Clinical Trials* 1998;19:61 – 109.

Representative NHLBI Research Projects Supported in FY 2000:

Project No.	Title	Investigator	Institution
R01 HL28266	Epidemiology of Cardiovascular Risk Factors in Women	Kuller	U. Pittsburgh

A long-term investigation of the evolution of cardiovascular risk factors and subclinical cardiovascular disease from premenopause through menopause.

P01 HL45666	Cardiovascular Benefits of Soy Phytoestrogens	Clarkson	Wake Forest U.

A group of studies focused on the potential cardiovascular benefits of soy photoestrogen supplementation/treatment.

U01 HL50840	Postmenopausal Hormone Replacement Therapy After CABG	Ouyang	Johns Hopkins U.

A clinical trial testing the hypothesis that postmenopausal HRT in women following coronary bypass surgery will reduce the occurrence of graft occlusion and delay the development of graft atherosclerosis.

R0l HL57790	CVD Risk & Health in Postmenopausal Phytoestrogen Users	Kritz-Silverstein	U. Cal., San Diego

A study to determine the acceptability and benefits of use of a dietary supplement of phytoestrogen (genistein) versus placebo on heart disease risk factors, bone density, and psychosocial outcomes in postmenopausal women.

R01 HL59331	Gender and Menopause on Nutrient And Energy Metabolism	Horton	U. Colorado

An investigation of gender-specific aspects of energy and nutrient metabolism and how they change at menopause.

R01 HL60739	Mutations, Hormone Therapy and Venous Thromboembolism	Psaty	U. Washington

An assessment of the interaction between HRT and prothrombotic mutations as it affects the incidence of venous thromboembolism.

R01 HL63293	Thrombotic, Inflammatory, & Gene Markers of CVD in Women	Ridker	Brigham & Women's Hospital

A substudy of the WHI observational study exploring inherited and environmental determinants of coronary thrombosis.

P50 HL63494	SCOR in Ischemic Heart Disease: Estrogen Receptor Modulation–Effects In Postmenopausal Women	Udelson	New Engl. Med.. Ctr.

An investigation of the hypothesis that the genetics, expression, and function of cardiovascular estrogen receptors and estrogen-regulated target genes mediate protection against ischemic diseases and their sequelae.

R01 HL65367	Estrogen, Inflammation and Atherosclerosis	Herrington	Wake Forest U.

A follow-up to the NHLBI-sponsored Heart and Estrogen/Progestin Replacement Study (HERS) to clarify the effects of HRT use on vascular inflammation and the consequences of these effects with respect to the pathogenesis of atherosclerosis.

R01 HL65531	Sex Steroid Hormones and Risk of CHD in Women	Rexrode	Brigham & Women's Hospital

An evaluation of the relationship between endogenous estrogen and androgen levels and risk of coronary heart disease among women in the WHI observational study.

Multiproject	Prevalence & Progression of Subclinical Atherosclerosis		

A determination of the extent to which diminishing ovarian function affects vascular function and accelerates the development of atherosclerosis in the coronary arteries, aorta, and carotid arteries.

R01 HL32050	Caffeine Influences on Exercise and Psychological Stress	Lovallo	U. Oklahoma

An evaluation of the effects of caffeine intake on blood pressure and cortisol secretion, under conditions of mental and exercise stress, with an emphasis on variations in response as women enter menopause.

R01 HL33177	Positron Tomography in Ischemic Heart Disease	Schelbert	UCLA

A study of coronary vasomotor function that, in postmenopausal women, will explore protective effects of estrogens against coronary atherosclerosis and examine whether these effects are negated or modified by progestins, as well as whether adequate protection requires addition of statins and antioxidants.

R01 HL34594	Risk Factors for Cardiovascular Disease In Women	Manson	Brigham & Women's Hospital

Continued follow-up of the Nurses Health Study cohort, first recruited in 1976, to evaluate hypotheses regarding dietary and hormonal risk factors for coronary heart disease and ischemic and hemorrhagic stroke.

R01 HL56144	Smoking, Estrogen and Cardiovascular Health in Women	Girdler	U. North Carolina

An examination of the differential effectiveness of transdermally administered estrogen versus orally administered estrogen in reducing cardiovascular disease risk in women who smoke.

P50 HL63494	SCOR in Ischemic Heart Disease: Cardiac Estrogen Receptors & MI	Karas	New Engl. Med. Ctr.

An investigation of the hypothesis that the genetics, expression, and function of cardiovascular estrogen receptors and estrogen-regulated target genes mediate protection against ischemic diseases and their sequelae, including vascular dysfunction, post-myocardial infarction remodeling, and arrhythmias.

Multiproject	Women's Angiographic Vitamin And Estrogen (WAVE)

A study to determine whether HRT and/or antioxidant treatment will stabilize and inhibit progression, or induce regression, of atherosclerotic plaques.

RECENT REPRESENTATIVE PUBLICATIONS

1. Matthews KA et al. Influence of estrogen replacement therapy on cardiovascular responses to stress of healthy postmenopausal women. Psychophysiology 2001 May;38(3):391-8.

2. Psaty BM et al. Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. JAMA 2001 Feb 21;285(7):906-13.

3. Light KC et al. Hormone replacement improves hemodynamic profile and left ventricular geometry in hypertensive and normotensive postmenopausal women. J Hypertens 2001 Feb;19(2):269-78.

4. Carlson CL et al. Hormone replacement therapy is associated with higher FEV1 in elderly women. Am J Respir Crit Care Med 2001 Feb;163(2):423-8.

5. Grodstein F et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000 Dec 19;133(12):933-41.

6. Gardner CD et al. Population frequency distributions of HDL, HDL(2), and HDL(3) cholesterol and apolipoproteins A-I and B in healthy men and women and associations with age, gender, hormonal status, and sex hormone use: the Stanford Five City Project. Prev Med 2000 Oct;31(4):335-45.

7. Pettiti DB et al. Hormone replacement therapy and the risk of myocardial infarction in women with coronary risk factors. Epidemiology 2000 Sep;11(5):603-6.

8. Herrington DM et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med 2000 Aug 24;343(8):522-9.

9. Lissin LW & Cooke JP. Phytoestrogens and cardiovascular health. J Am Coll Cardiol 2000 May;35(6):1403-10.

NATIONAL INSTITUE ON AGING

(NIA)

National Institute on Aging

Endocrine Aging Changes

Sherry Sherman, Ph.D

Significance of Program Area

Reproductive aging and its consequences are topics of high relevance in both men and women. In the next two decades, approximately 40 million American women will experience the menopause. Menopause is a universal phenomenon of women, yet, it is incompletely understood. Furthermore, much of what is known is based on data from Caucasian women, from women who are self-referred to menopause clinics, or from convenience samples of women seen in clinical settings for other health problems. Although hot flashes are the hallmark of the menopause transition, the cause, predictors, racial/ethnic distribution and natural history of these symptoms remain poorly characterized. In men, knowledge on the causes and consequences of age-related changes in circulating reproductive hormones is also very limited. In addition to understanding the short-term concomitants of menopause, more research is needed on the long-term consequences of reproductive aging in both men and women in order to differentiate normal or usual aging from successful aging and to capitalize on factors predictive of health and increased longevity.

Program Activities

The NIH Workshop on Selective Estrogen Receptor Modulators (SERMs), held April 26-28, 2000 was led by the National Institute of Aging (GP, BAP, NNA) in collaboration with NCI's Division of Cancer Prevention, and other government components (NHLBI, NIAMS, NICHD, NIDCR, NIDDK, NIEHS, the Office of Research on Women's Health, NIH and the Office of Women's Health, DHHS.) The overarching objectives of this workshop were to identify pivotal questions and formulate future projects in SERM research that cross disease boundaries and potentially incorporate multiple disease endpoints up front. This collaborative effort pulled together SERM experts from basic and clinical sciences bridging many physiological systems and multiple institutes as well as pharmaceutical companies, the FDA, and legal and regulatory affairs offices.

Key conclusions from this workshop include:

1. Future basic science research should address the mechanism of SERM action. Research should focus on the estrogen receptor (ER) and its cofactors as the basis for the discriminatory activity of estrogen and different SERMs in different tissues as well as for the development of SERM (i.e., tamoxifen) resistance. The ER (both ERα and ERβ) is drug discovery target to elucidate these mechanisms in the search for novel SERMs.

2. The search for novel SERMs must emphasize agents that exhibit efficacy across multiple disease endpoints and at the same time do not have the toxicity of current SERMs. Future clinical trials should be designed prospectively to include multiple disease endpoints.

Building Interdisciplinary Research Careers in Women's Health (RFA-OD-99-008; http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-99-008.html). GP contributed topics on menopause and the chronic diseases of aging to an RFA using the NIH Mentored Research Scientist Development Program Award (K12) mechanism. Released in the NIH Guide on September 7, 1999, the objective of the RFA was to support research career development of junior faculty members who have recently completed clinical training or postdoctoral fellowships, and who are commencing basic, translational, clinical and/or health services research relevant to women's health.. GP cofunded two of these K12 awards in the summer of 2000 for a period of five years.

New Grants Funded. GP also funded two randomized controlled trials. We are working with both principal investigators in setting up DSMBs.

"DHEA Replacement In Healthy Older Men and Women" to be conducted at UC San Diego, will evaluate the acceptability, benefits, adverse effects, and metabolism of daily oral DHEA replacement for one year in men and women ages 55-85 years. A wide range or biological outcomes will be studied including bone mineral density and metabolism, body composition and muscle strength, immune function, and cardiovascular risk factors. Central effects of DHEA will be investigated by assessing changes in mood and well-being, cognitive function, and sexuality.

"Alternative Therapies For Menopause" will investigate the efficacy and safety of three alternative approaches utilizing phytoestrogens to treat vasomotor symptoms in peri- and postmenopausal women. The five proposed treatment arms are as follows: 1) esterified estrogen and micronized progesterone: 9) a single herbal product, black cohosh; 3) a multibotanical preparation; 4) a combination regimen that includes the same multibotanical preparation plus soy diet counseling; and 5) placebo. The study will be conducted at the Group Health Cooperative of Puget Sound.

"Progestogens vs. Phytoestrogens: An Adjunct to ERT" proposes to test whether soy phytoestrogens (SPEs) may be able to replace progestogens in hormone replacement therapy (HRT) as a better alternative for the prevention of estrogen-associated endometrial hyperplasia. It will also evaluate potential SERM-like effects of SPEs in antagonizing the mammary effects of estrogen and the synergistic effects of SPEs with estrogen with respect to cardiovascular and bone endpoints.

"The SWAN Repository" was funded at the University of Michigan. This grant supports the development of an infrastructure for the ongoing maintenance and utilization of a repository of serum, plasma, urine and DNA specimens collected from SWAN participants. GP staff are participating in this new component of the SWAN cooperative agreement in the establishment of the SWAN Repository Advisory Committee and in other related activities.

"Functional Status And The Menopausal Transition" will study the natural history and the role of the menopausal transition in the development of functional limitations in 500 middle-aged African American and Euro-American women participants at the University of Michigan SWAN field site.

Study of Women's Health Across the Nation (SWAN). Funded initially in September 1994, SWAN is supported by NIA (GP and BSR), the National Institute of Nursing Research (NINR), NHLBI, ORWH, NIMH, and the National Center for Complementary and Alternative Medicine (NCCAM).

To more fully understand the menopausal transition in socially and culturally diverse women, the specific aims of SWAN are: 1) to describe the symptoms, hormones and bleeding patterns of the menopausal transition; 2) to relate these patterns to change in markers for osteoporosis, heart disease, diabetes, and amount of fat and lean; 3) to relate personality and behaviors, including life style behaviors, to age at onset, symptoms and physical changes of the transition; 4) to consider what are menopause-related changes and what are age-related changes; and finally, 4) to describe cultural and ethnic differences among women with respect to their mid-life aging and the menopausal transition. SWAN is a prospective, multi-center, multi-ethnic, multi-disciplinary study of the natural history of the menopausal transition. The overall study design includes a cross-sectional study and a longitudinal cohort study using common protocols at the seven sites with clinical examination facilities. Two additional sources of data, the monthly menstrual cycle calendars and daily specimen/diary collection, are critical in more precisely characterizing the menopause. A variety of methods used to recruit this sample of multi-ethnic women. A total of 202,985 households or telephone numbers were screened for women eligible for participation in the SWAN Cross-sectional Study and 16,065 women were eligible and completed the interview. Of these, 6,521 women were cohort-eligible and asked to participate in the SWAN Longitudinal Study; a total of 3,306 women entered the Longitudinal Study. [**MF Sowers, University of Michigan, Ann Arbor**; **R01 AG17104** in conjunction with the following grants comprising SWAN: U01 AG12505, U01 AG12531, U01 AG12535, UO1 AG12539, U01 AG12546, U01 AG12553, U01 AG12554, U01 NR04061, UO1 AG 12495, U01 AG 17719, R01 AG17104].[d]

1. Since last year, nine manuscripts were published or are in press and an additional 12 were submitted for publication using the cross-sectional, screener data.

2. In the longitudinal phase, a cohort of premenopausal women from the cross-sectional phase were enrolled. They were aged 42-52, "at risk" for a natural menopause [i.e., with a uterus plus at least one intact ovary], menstrual period within the past three months and taking no hormone medications. Enrollment for the baseline, first and second follow-up visits were completed in 1997, 1998 and 1999, respectively. The third and fourth rounds of follow-up visits are currently in the field.

[d] Sowers MF**, Crawford S, Sternfeld B, Morganstein D,** Gold E**,** Greendale GA**, Evans D,** Neer R, Matthews K**, Sherman S, Lo A,** Weiss G**, Kelsey J. SWAN: A Multi-Center, Multi-Ethnic, Community-Based Cohort Study of Women and the Menopausal Transition. In:** Menopause**. Eds., Lobo R, Marcus R, Kelsey J. New York: Academic Press 2000.**

Research Advances

Menopausal symptoms: role of demographic and lifestyle factors. SWAN entered the field with a community-based survey during 1995 -1997 to study factors related to menopausal and other symptoms in a multi-racial/ethnic sample of 16,065 women aged 40-55 years. Each of seven sites surveyed one of four minority populations and a Caucasian population. The highest prevalence of hot flashes and night sweats was among women who had begun the menopausal transition (peri-menopause) as evidenced by the occurrence of their period being more unpredictable or in women who were post-menopausal. These women reported hot flashes or night sweats two to four times as often as premenopausal women whose periods were still regular. Japanese and Chinese women were least likely to report any symptoms. African American women were more likely than other women to report hot flashes or night sweats and vaginal dryness but less likely to report urine leakage or difficulty sleeping. Hispanic women were more likely than other women to report urine leakage, vaginal dryness, heart pounding or racing and forgetfulness. More stiffness and soreness, urine leakage, and hot flashes or night sweats were reported by women with greater weight for their height, for example weighing more than 152 pounds for women who were 5 foot 4 inches tall. All symptoms were also reported most frequently among women who had difficulty paying for basics, who were currently smokers or who reported that they were less physically active than other women of their own age. These results suggest that lifestyle, menstrual status, race/ethnicity and socioeconomic status affect symptoms in this age group. The results of the SWAN cross-sectional survey indicate that a number of potentially modifiable factors affect symptomatology. Thus, for women for whom medical treatment is contraindicated or cannot be tolerated, alternatives may be promising in lifestyle changes.[**E. Gold, University of California at Davis; U01 AG 12554** in conjunction with the following grants comprising SWAN: U01 AG12505, U01 AG12531, U01 AG12535, UO1 AG12539, U01 AG12546, U01 AG12553, U01 AG12554, U01 NR04061, UO1 AG 12495, U01 AG 17719, R01 AG17104].[e]

Which are "true" menopausal symptoms? A variety of symptoms including hot flashes, night sweats, menstrual irregularities, vaginal dryness, as well as depression, irritability, tension, and dizzy spells are often assumed to cluster together as women experience menopause. Taken together, these symptoms have been proposed to be the various components comprising a "menopausal syndrome." Although some research has suggested that psychological symptoms are not really part of menopause, most of this research has been conducted primarily among Caucasian women and even in these women, the role of menopause in psychologic symptomatology remains controversial. To better understand the diversity of the menopause experience, the consistency of various symptoms as components in menopause-related symptomatology was evaluated in this ethnically and racially diverse group of SWAN women. Using the statistical method of factor analysis, two consistent factors emerged across all racial/ethnic groups: one consisting of clearly menopausal vasomotor symptoms – hot flashes

[e] **Gold, E. B**., Sternfeld, B., Kelsey, J. L., Brown, C., Mouton, C., Reame, N., Salamone, L., Stellato, R. The relation of demographic and lifestyle factors to symptoms in a multi-ethnic population of 40-55 year old women**. Am J Epidemiol**. 2000; 152:463-73

and night sweats – and the other consisting of psychological and psychosomatic symptoms. After controlling for confounders such as age, education, health, etc. it was observed that Caucasian women reported significantly more psychosomatic symptoms than other groups, while African American women reported significantly more vasomotor symptoms. Perimenopausal, postmenopausal women and women with a surgical menopause all reported significantly more vasomotor symptoms than premenopausal women. The pattern of results argues against a universal menopausal syndrome consisting of the combination of both vasomotor and psychological symptoms. [**S. McKinlay, New England Research Institutes, Watertown, MA; UO1 AG 12553** in conjunction with the following SWAN grants: U01 AG12505, U01 AG12531, U01 AG12535, UO1 AG12539, U01 AG12546, U01 AG12554, U01 NR04061, UO1 AG 12495, U01 AG 17719, R01 AG17104][f]

Osteoarthritis Onset Occurs Earlier, in Middle-Aged African American And Caucasian Women at one SWAN field site. [**MF Sowers**, University of Michigan, Ann Arbor; R01 AG17104].[g] See Section on Highlights of Major Scientific Advances.

Hearing impairment affects substantial numbers of middle-aged women. Another study of SWAN African-American and Caucasian women living in Michigan was conducted to determine the percentage of women who had clinically-assessed, high-frequency hearing impairment (HFHI) and self-reported hearing impairment (SRHI) and, importantly, the association of these hearing assessments with physical and mental functioning. It was determined from independent evaluation that almost 27% (n=124) of these middle-aged women had hearing impairment in at least one ear and 12% (n=56) had hearing impairment in both ears. Hearing impairment was self-reported by 16.7% (n=78) of the women, with few of the women who tested with hearing impairment also self-reporting hearing impairment (n=36). Examination of the association of hearing impairment with functioning showed that HFHI in one ear only was not significantly associated with either physical or mental functioning. However, HFHI in both ears was significantly associated with mental functioning while SRHI was significantly associated with limitations in both physical and mental functioning. The poor relationship of HFHI and SRHI in this population, combined with the significant association of SRHI with both measures of functioning indicates that these two methods of assessing hearing impairment may be measuring different aspects of the impairment. Obtained self-reported hearing impairment information may facilitate early identification of individuals with hearing-related functional limitations. [**MF Sowers,** University of Michigan, Ann Arbor; R01 AG17104-01A1][h]

Attitudes and the experience of menopause. Menopause is a psychosocial as well as a biological event. Attitudes, perceptions, and expectations are part of the psychosocial

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[f] Avis N, Stellato R, Bromberger J, Crawford S, Ganz P, Kagawa-Singer M. Is there a Menopausal Syndrome? Menopausal Status and Symptoms Across Racial/Ethnic Groups. **Social Science and Medicine** 2000.

[g] **Sowers MF**, Lachance L, Hochberg M, Jamadar D. Radiographically-defined osteoarthritis of the hand and knee in young and middle-aged African American and Caucasian women. **Osteoarthritis Cartilage** 2000; 8:69-77.

[h] Pope, S. K., **Sowers, M. F**., Functional Status and Hearing Impairments In Women at Mid-Life. **J Gerontol: Social Sciences**, 55B(3): S190-194, 2000.

phenomena surrounding menopause. In analyses conducted to evaluate the role of race/ethnicity and menopausal status on attitudes toward menopause, it was found that in general, women's attitudes toward menopause range from neutral to positive. African-American women expressed the most positive attitudes toward menopause and aging. The least positive groups were the Chinese- and Japanese-speaking women who received their schooling outside of the US – i.e., women who had less exposure to American culture. Whether a woman was pre- or post-menopausal (or in the middle of the transition) did not make a noticeable difference in attitude. Because it is known that attitudes play a role in the experience of menopause, understanding the determinants of positive attitudes may be valuable in ultimately promoting smooth and healthy transitions to postmenopause. [**E. Gold, University of California at Davis; U01 AG 12554** in conjunction with the following SWAN grants: U01 AG12505, U01 AG12531, U01 AG12535, UO1 AG12539, U01 AG12546, U01 AG12553, U01 AG12554, U01 NR04061, UO1 AG 12495, U01 AG 17719, R01 AG17104].[i]

Markers of Menopause Status. Accurately staging the various phases in the transition from pre- to postmenopause is necessary and compelling in family planning, identifying potential health issues and for defining populations of women of late-reproductive age for research. Currently, it is only possible to categorize a woman as menopausal after 12 months of amenorrhea, with no ability to reliably identify any interim stages of reproductive aging. As part of a long-term effort to develop new biochemical assays to stage women during the perimenopausal transition, investigators examined the patterns of urinary excretion of a metabolite of luteinizing hormone (LH) known as heterodimeric luteinizing hormone beta core fragment (hLHßcf) in premenopausal, perimenopausal, and postmenopausal women. In a collaboration involving three different GP/NIA grantees, measurements were made of the concentration of this metabolite in consecutive first morning void urine specimens from premenopausal, perimenopausal, and postmenopausal women. Day 1 of collection was the first day of menses in the cycling women. Analyses showed that postmenopausal women exhibited a widely fluctuating pattern of LH beta core fragment excretion, which is not correlated with the parent hormone, hLH, or with follicle-stimulating hormone (FSH). The pattern of excretion and concentrations of the hLHßcf was observed to be significantly different between premenopausal and postmenopausal women. The postmenopausal group was easily distinguished from premenopausal women on the basis of an area-under-the-curve concentration function. Perimenopausal women displayed intermediate hLHßcf changes or concentrations; some clearly were in postmenopausal ranges, and others were in the premenopausal ranges. The capability to evaluate this type of stable urinary metabolite as a reflection of changes in the dynamics of its parent circulating hormone offers new possibilities in staging the menopause and in the development and application of large-scale testing that does not require blood sampling. Validation and verification of such an advance could have significant clinical benefits and benefits in properly defining populations for research. [**S. Birken,** Columbia University College

[i] Sommer, B., Avis, N., Meyer, P., Ory, M., Madden, T., Kagawa-Singer, M., Mouton, C., Rasor, N. O., & Adler, S. Attitudes toward menopause and aging across ethnic/racial groups. **Psychosomatic Medicine** 61(6): 868-875, 1999.

of Physicians and Surgeons, New York; AG13783; **N. Santoro**, Albert Einstein College of Medicine, New York, AG12222; **E. Freeman,** U. Pennsylvania, Philadelphia; AG12745][j]

Future Directions

Selective Estrogen Receptor Modulators (SERMs). We continue to maintain and strengthen our collaborations with the cooperating institutes that participated in the NIH Workshop on the SERMS in publishing the proceedings of the workshop and a program announcement to encourage basic and clinical research initiatives. Our ongoing working group will continue to focus on identifying critical areas of SERM research and formulating collaborative research activities that that encompass multiple disease endpoints.

Staging the Menopause. GP staff will convene an "NIH Workshop on Staging the Menopause." in late Spring 2001. In addition to NIA (GP, BAP), and NICHD, the workshop will be co-sponsored by the American Society for Reproductive Medicine (ASRM) and the North American Menopause Society (NAMS). The overarching goal is the identification of a logical division of the last 10 to 15 years of hypothalamic-pituitary-ovarian function in women into stages that would be relevant to the research community with possible clinical relevance as well. It is assumed the basis for these stages would be primarily clinical (e.g., menstrual cycle) and endocrinologic (e.g., FSH, etc.) changes that normally occur as a normal woman progresses through her latter years of reproductive function prior to culmination at menopause. Other factors could be taken into account such as vasomotor symptoms, duration or intensity of menstrual flow, etc.

Background. Reproductive aging is a continuum from birth to menopause. The physiologic basis is follicular /oocyte depletion in the ovary. In Western civilization the average age of menopause is 50, with a moderately wide range (42-58 years). The most obvious manifestation of reproductive (ovarian) function for women is menstrual cyclicity. A normal woman will have regular menstrual cycles well into her forties. A subtle sign of reproductive aging that precedes the first irregular menstrual period is a shortening of the menstrual cycle from an average of 28 to approximately 23-25 days. This is ultimately followed by irregular cycles, episodes of amenorrhea, and finally permanent amenorrhea (menopause).

The problem. When research is performed in different locations by different investigators, the populations studied tend to be somewhat different. This is especially true when attempts are made to study a continuum such as in the case of reproductive aging. Considering the variability in the age of menopause, there will be inevitable biologic heterogeneity in a given advanced reproductive age (ARA) population at a particular chronologic age (e.g., 45 years). Given this intrinsic population heterogeneity and different selection criteria employed by different research groups, it has been difficult to compare the findings from one ARA study to another. The attempts to date to define the spectrum of reproductive aging have only addressed nomenclature. In 1996, the World Health Organization published a technical report entitled, "Research on the

[j] **Birken S**, **Santoro N**, Maydelman Y, Kovalevskaya G, Lobo R, **Freeman EW,** Warren M, McMahon D, O'Connor J. Differences in urinary excretion patterns of the hLH beta core fragment in premenopausal, perimenopausal, and postmenopausal women. **Menopause** 1999;6:290-8.

Menopause in the 1990s." In this monograph they attempted to organize the terminology around the menopause but failed to clarify an already confused set of terms. For instance, they continued to use three terms to refer to the years immediately preceding the menopause: 1) menopausal transition, 2) perimenopause, 3) premenopause. Based on today's terminology, confusion abounds as to where a women or group of women lie on a continuum of reproductive aging.

Developing a staging system for research purposes is compelling and necessary. A relevant analogy would be the Tanner/Marshall stages of pubertal development. When Tanner and Marshall presented their clinical staging system for breast and pubic hair development to define female puberty more than 50 years ago, it quickly became the standard. To those who are not familiar with this staging system, there are five stages for breast and pubic hair development that reflect adrenal and ovarian function. While there is heterogeneity among populations and biologic variability in the presence and duration of these pubertal stages, nevertheless, this system enables the classification of a study population for comparison of findings and conclusions.

Osteoporosis

Sherry Sherman, Ph.D.

Significance of Program Area. Osteoporosis is a condition characterized by increased skeletal fragility and susceptibility to fractures. A significant cause of frailty, morbidity and even mortality, osteoporosis and its consequences -- particularly vertebral and hip fractures -- are a serious public health problem in the aging population. Although the development and FDA approval of new therapeutic agents offer great promise for reducing bone loss and osteoporotic fractures, identifying individuals at risk for this disease and preventing fractures still remains a considerable challenge. Differences in fracture rates appear to be mediated by a number of intrinsic and extrinsic factors governing bone structure and quality, bone metabolism and the accretion and preservation of skeletal mineral mass. These factors include gender, racial/ethnic and genetic aspects, hormone status, use of estrogen and other medications (e.g.,, thiazide diuretics), nutritional intake and metabolism (e.g. of calcium and vitamins D and K) and other lifestyle influences (e.g., physical activity) which govern bone metabolism and bone mineral retention.

Program Activities

"**Androgens and Bone" Newer Perspectives on Mechanisms and Management**" was the focus of the *Sixth Annual Meeting of the Working Group on Aging and the Human Skeleton* (September 23, 2000 at the American Society for Bone and Mineral Research (ASBMR) 22nd Annual Meeting, Toronto, Canada.) This working group was organized by Pam Robey of NIDR, Cliff Rosen (St. Joseph's Hospital, ME) and S. Sherman. One major objective of the *Working Group on Aging and the Human Skeleton* is to address methodological issues integral to facilitating clinically relevant studies on the causes and consequences of bone loss and osteoporosis as it occurs at the cellular and tissue levels in mature humans. Topics which were

presented included "Androgen, Estrogen or Aging? What's New about the Old Male Skeleton," (Dr. Stavros Manolagas), "Androgens and their Direct Effects on Osteoclasts" (Dr. Wes Pike), "DHEA and Bone Mass – A New Treatment Paradigm for Elders?" (Dr. Meryl LeBoff) and "Marrow Stromal Cells, Senescence, and DHEA," Dr. Julie Glowacki.

The "**ASBMR New Investigator Breakfast**" was convened on September 22 at the 2000 ASBMR Annual Meeting to provide new investigators with an opportunity to discuss current and future research directives, training and prospects of funding with representatives of CSR, DOD, NASA, and NIH institutes (NIA, NIAMS, NICHD, NIDDK, NIDCR and NCI) that support research in the field of bone and mineral research.

Writing Groups for *STOP/IT.* Primary outcome papers from two randomized controlled trials from the cooperative agreement, ***STOP/IT,*** are in preparation with S. Sherman participating as an author.

"The Effect of Hormone Therapy And Calcitriol Given Alone And In Combination On Bone Mineral Density in Elderly Women." Analyses show that in a group of elderly women (age 65-77), with normal bone density for their age, that estrogen was highly effective in reducing bone turnover and increasing bone mineral density (BMD) at the hip and other clinically relevant sites. Importantly, the group receiving the estrogen and calcitriol combination realized the most rapid and greatest gains in BMD. Reductions in the number of falls and a trend toward reduced fractures in the calcitriol-only group suggest that this agent may be important to include in regimens in future prevention studies aimed at rapidly increasing BMD and reducing the risk of osteoporotic fractures. [JC Gallagher, Creighton University, U01 AG10373).

"Effect of Home-based Weight-bearing Exercise on Femoral Neck Bone Density in Older Men and Women." In this study, men and women 65-78 years of age who performed two years of a simple, home-based, bench step exercise program showed significantly reduced bone loss compared to the placebo group. [Gail Dalsky, University of Connecticut, U01 AG10382]

Studies requiring substantial program oversight

"Osteoporosis in Men," (a.k.a. **Mr. OS**) is a multicenter prospective study of risk factors for vertebral and non-vertebral fractures in older men which was funded as a cooperative agreement in September 1999 by NIAMS, NIA and NCI. A total of 5,700 men, aged 65 years and older will be recruited from the populations of six cities across the U.S. The primary goal of Mr.OS is to determine the extent to which fracture risk in older men is related to bone mass, bone geometry, lifestyle factors, biochemical measures, fall propensity, and other variables. This information is essential for understanding the genesis of fractures, and for the formulation of clinical algorithms for detection and treatment of osteoporosis in men. A second goal is to determine the relationship between osteoporotic fracture and prostate cancer. During the past year S. Sherman participated as a member of the Steering Committee in the development of study procedures and protocols [S. Cummings, UCSF, U01 AG-18197-02].

"Calcium And Vitamin D Malnutrition In Elderly Women" is a randomized controlled trial at Creighton University which is designed to test whether calcium supplementation alone

(1500mg/d) or calcium 1500mg/d) plus vitamin D (800IU/d) reduces the incidence of fractures, eliminates secondary hyperparathyroidism, and halts bone loss in a large population-based sample of 1200 women 60+ years of age. GP staff worked closely with the principal investigator in setting up and convening the DSMB and incorporating DSMB input into the procedures and conduct of the study [J. Lappe, Creighton U; R01 AG 14683-02]

"**Genetic Determinants Of Bone Fragility**." The overarching goal of the program project is to identify chromosomal regions that harbor genes that affect the components of bone fragility and predispose to fractures. The investigators will use non-parametric linkage analysis techniques in a large sample of 1400 Caucasian and African American pre-menopausal sister pairs to map, and ultimately clone, genes that play important roles in determining peak BMD. They will also assess bone strength in 700 pairs of brothers, compare heritabilities to those of the 760 pairs of sisters, and conduct a genomic screen to identify loci that influence bone strength in men. Parallel studies will be conducted in Fischer 344 rats. S. Sherman worked with the PI in identifying individuals for an advisory panel which will provide input on methodological, procedural and human subject issues. [M. Econs, University of Indiana; P01 AG18397]

Research Advances

Hydrochlorothiazide and Preserving Skeletal Integrity: a randomized, controlled trial in men and women. [**A. LaCroix**, Group Health Cooperative of Puget Sound, Seattle: AG09825][k] See Section on Highlights of Major Scientific Advances.

Women with high blood pressure have greater rates of bone loss. Hypertension is associated with abnormalities in calcium metabolism. Sustained calcium loss may lead to elevated parathyroid hormone levels and increased bone-mineral loss in people with high blood pressure. This study evaluated the prospective association between blood pressure and bone-mineral loss over time in elderly white women.: A subset of 3676 women from the Study of Osteoporotic Fractures (SOF) who were not on thiazide diuretics were studied. Their mean age was 73 years [range 66-91 years], mean bodyweight 65.3 kg and blood pressure 137/75 mm Hg. Anthropometry, blood pressure, and bone-mineral density (BMD) at the femoral neck were measured at baseline and bone densitometry was repeated after 3.5 years by dual-energy X-ray absorptiometry. After adjustment for age, initial BMD, weight and weight change, smoking, and regular use of hormone-replacement therapy, it was determined that the rate of bone loss at the femoral neck increased with increasing blood pressure at baseline. In the quartiles of systolic blood pressure, yearly bone losses increased from 2.26 mg/cm2 in the first quartile to 3.79 mg/cm2 in the fourth quartile (test for linear trend, p=0.01), equivalent to yearly changes of 0.34% and 0.59%. There was no significant interaction with age. The exclusion of women on antihypertensive drugs did not alter the results. For diastolic blood pressure, there was an association with bone loss in women younger than 75 years. Higher blood pressure in elderly white women is associated with increased bone loss at the femoral neck. This association may reflect greater calcium losses associated with high blood pressure, and may contribute to an enhanced risk of hip fractures. Strategies which can control high blood pressure (such as

[k] **LaCroix AZ**, Ott SM, Ichikawa L, Scholes D, Barlow WE. Low dose hydrochlorothiazide and preservation of bone density in older adults: results of a three-year randomized controlled trial. Ann Intern Med 2000;133:516-26.

restriction of sodium intake and thiazide diuretics) and also reduce calcium losses should be explored further for their ability to reduce bone loss and prevent osteoporotic fractures. [**S.R. Cummings,** University of California San Francisco; R01 AG05407 and **K. Ensrud,** University of Minnesota, Minneapolis; R01 AG05394][l]

Low Fractional Calcium Absorption Increases the Risk for Hip Fracture in Women with Low Calcium Intake. [**KE Ensrud**, University of Minnesota, Minneapolis**:** AG05394 and **SR Cummings**, University of California at San Francisco: AG05407][m] See Section on Highlights of Major Scientific Advances.

Low Vitamin K intake increases the risk of hip fractures. Vitamin K has been associated with bone mineral density (BMD) and risk of hip fracture. The apolipoprotein (apo) E4 allele (APOE*E4) has been associated with bone fracture through a putative effect on vitamin K transport in blood. This analysis was conducted to determine the relationships of vitamin K intake, apo E genotype, BMD, to hip fracture in a population-based cohort of elderly men and women. Dietary vitamin K intake was assessed with a food-frequency questionnaire in 335 men and 553 women (average age: 75.2 years) participating in the Framingham Heart Study in 1988-1989. The incidence of hip fractures was recorded from 1988 to 1995 and BMD at the hip, spine, and arm was assessed on 2 separate occasions (from 1988-1989 and from 1992-1993). The investigators found that after adjustment for age, weight, physical activity, calcium intake and other confounders, the risk of hip fracture was significantly reduced by 65% in individuals in the highest quartile of vitamin K intake (median: 254 microgram/day) compared to those in the lowest quartile of intake (median: 56 microgram/day). In this study, there were no associations between vitamin K intake and BMD or change in BMD in either men or women. No association was found between the E4 allele and hip fracture, BMD or changes in BMD. BMD is an important determinant of bone quality. However, although low BMD plays an important role in increasing the risk of hip fracture, other factors which influence bone quality (and which may be independent of BMD), such as hip geometry and architecture, may be significantly influence the risk of hip fracture. Because inadequate vitamin K intake may influence the quality of the matrix or scaffold upon which bone mineral is deposited, low vitamin K intake may be an important unrecognized factor which increases the risk of hip fracture in elderly men and women.. The effectiveness of interventions with supplemental vitamin K where dietary intake is inadequate should be explored further as they may be highly cost effective in reducing these calamitous events. **[D. Kiel,** Hebrew Rehabilitation Center for the Aged, Boston; R01 AR/AG 41398-08].[n]

Bone loss during the menopause transition is increased in women with the APOE*4 allele. The identification of genes that contribute to bone mineral density (BMD) and bone loss has

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[l] Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA. High blood pressure and bone-mineral loss in elderly white women: a prospective study. Study of Osteoporotic Fractures Research Group. Lancet 1999;354:971-5.

[m] **Ensrud KE**, Duong T, Cauley JA, Heaney RP, Wolf RL, Harris E, Cum**mings SR**. Low fractional calcium absorption increases the risk for hip fracture in women with low calcium intake. Ann Intern Med 2000; 132:345-53.

[n] Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, Cupples LA, Wilson PW, Ordovas J, Schaefer EJ, Dawson-Hughes B, **Kiel DP**. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. Am J Clin Nutr 2000;71:1201-8.

widespread implications for the understanding and prevention of osteoporosis. The objective of this study was to examine the relationship between the presence and absence of the apolipoprotein E*4 (APOE*4) allele and both BMD and rate of change in BMD at the lumbar spine and hip in a population of 392 healthy, pre-, peri-, and postmenopausal white women participating in the Women's Healthy Lifestyle Project. BMD at the lumbar spine and hip was measured at baseline and after a mean of 2.5 years using dual-energy X-ray absorptiometry (DXA). In premenopausal women, there were no significant differences in BMD or in the annualized rate of change in BMD at the spine or hip when comparing women with and without the APOE*4 allele. In contrast, spine bone loss was significantly greater in peri- and postmenopausal women having an APOE*4 allele than in women without this allele (-1.75% vs. -0.98% per year, respectively, $p = 0.018$). Among peri- and postmenopausal women currently using hormone replacement therapy (HRT), there were no differences in the rate of change in spine BMD; whereas, among non-HRT users, there was a 2-fold higher rate of spine bone loss in women with an APOE*4 allele compared with women without this allele (-2.31% vs. -1.27 % per year, respectively, $p = 0.033$). This study shows the importance of APOE*4 allele in spine bone loss in peri- and postmenopausal women and, more importantly, it provides evidence for a genetic and lifestyle interaction in modulating spine bone loss. **[LM Salamone, University of Pittsburgh, AG13873][o]**

Paget's Disease of The Bone Linked to More Than One Gene. Paget's disease of the bone is a common skeletal disorder. Recently, a gene for Paget's disease was localized to a region of chromosome 18q. There is compelling evidence for a genetic basis of Paget's disease. In addition, a gene, localized to 18q, that has been linked to another metabolic bone disease, familial expansile osteolysis (FEO), was to be associated with Paget's disease. Subsequent research showed such linkage in five Paget's disease families. However, this linkage was not seen in three other Paget's disease families, indicating linkage heterogeneity. The investigators report the identification and clinical characterization of a large pedigree of Paget's disease and demonstrate that the Paget's disease gene in this pedigree is not linked to the region on 18q, thus confirming linkage heterogeneity. Genotyping and linkage analysis was performed on blood samples obtained from 54 members of another Paget's disease pedigree. Examination of markers flanking the FEO locus showed no evidence of linkage. Given that the locus in this family is not linked to the FEO and Paget's disease locus on 18q, the researchers conclude that the findings confirm evidence for linkage heterogeneity within this disease. This indicates that more than one gene may influence the development of this phenotype. Although there are indications of linkage between Paget's disease of the bone and a region of chromosome 18q, this is not the case in all affected families. **[Cohen; Duke University OAIC, P60AG-11268][p]**

Estrogen Stimulates Production of a Protein that Lessens Bone Loss.

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[o] **Salamone LM**, Cauley JA, Zmuda J, Pasagian-Macaulay A, Epstein RS, Ferrell RE, Black DM, Kuller LH. Apolipoprotein E gene polymorphism and bone loss: estrogen status modifies the influence of apolipoprotein E on bone loss. J Bone Miner Res 2000;15:308-14.

[p] Nance MA, Nuttall FQ, Econs MJ, Lyles KW, Viles KD, Vance JM, Pericak-Vance MA, Speer MC. Heterogeneity in Paget's disease of the bone. Am J Med Genet. 2000 Jun19;92(5):303-7.

[**BL Riggs**, Mayo Clinic, Rochester MN: AG04875][q] See Section on Highlights of Major Scientific Advances.

Future Directions

Combination Therapies to Combat Osteoporosis. Although several therapies (including calcium and vitamin D, estrogen, calcitonin, alendronate, raloxifene, risedronate) are efficacious in stemming bone loss, producing modest gains in bone mineral density and preventing fractures, the ability to markedly stimulate bone formation and increase bone mass in individuals with osteopenic or osteoporotic skeletons is very limited. Recent findings suggest that combination therapies such as a) estrogen + calcium + vitamin D, b) alendronate + estrogen, c) PTH + estrogen and d) estrogen + calcitriol may produce additive (or synergistic) effects resulting in more substantial gains in bone density. With many new single-agent therapies demonstrating efficacy, opportunities will be explored to determine the value of promoting research which combines two or more agents to produce more optimal gains in bone mass and fracture reduction, while reducing side-effects and improving safety.

[q] Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Spelsberg TC, **Riggs BL**. Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. Endocrinol 1999; 140:4367-4370.

NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

(NIDCR)

National Institute of Dental and Craniofacial Research

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to improve and promote craniofacial, oral, and dental health through research. To further our mission, we support research and research training in normal development as well as in oral diseases and disorders. The scope of the Institute's research includes acquired and congenital conditions, infectious diseases including periodontal diseases and dental caries, oral cancers, oral manifestations of HIV infections and chronic and disabling disorders such as bone and joint diseases and nuerological and neurosensory disorders with particular emphasis on chronic pain. Research advances that affect women in particular are found within a number of these broad research categories. Women are for example more likely to seek treatment for disorders marked by pain or dysfunction in the temporomandibular joint or surrounding masticatory muscles, more likely to experience salivary disorders such as Sjogren's syndrome, and to experience tooth loss associated with osteoporosis.

This report begins with a summary of progress on two NIDCR-supported projects which directly focus on oral biological changes in post menopausal women. Both of these projects are investigating oral bone loss, which may prove to provide an additional marker for overall bone loss. The second project is evaluating specific effects of hormone replacement therapy (HRT) on oral bone loss and tooth loss.

Other NIDCR-supported projects are evaluating the role of reproductive hormones in the neurobiology of pain transmission and modulation and in pain perception. These projects, while not directly focusing on menopause per se, are also included, since changes in hormonal status remains one of the defining changes occurring during menopause.

Summary of Findings directly Relevant to Menopause.

Oral Bone Loss in Post-Menopausal Women: The NIDCR supports a seven-year longitudinal study of osteoporosis and oral bone loss being conducted on a sub-sample of participants enrolled in the observational component of the NIH-supported Women's Health Initiative (WHI). As part of the study protocol, comprehensive medical history and examination data from the core WHI, including hip bone mineral densities (BMD) as determined by dual energy x-ray absorptiometry, are linked with oral examination results and oral bone density assessments derived from a validated technique known as digital subtraction radiography.

Cross-sectional analyses of baseline data indicate a strong and significant correlation between lower jaw and hip BMD ($r = 0.78$, $p < .001$). Preliminary analyses of data from the initial group of participants completing three-year follow-up appointment suggest that this association may be clinically important. Among participants with evidence of periodontal bone loss at baseline, those with hip BMDs greater than 1 standard deviation below the reference value for young healthy women had higher rates of progressive oral bone destruction as compared to participants with hip BMDs within one standard deviation of normal ($p < .05$).

Further studies are needed to determine the clinical implications of an association between oral and skeletal bone status, and whether oral cavity examination and radiographic findings may be useful signs of extra-oral bone diminution.

Effects of Estrogen Replacement Therapy (ERT) on postmenopausal changes in alveolar bone height and bone mineral density An ongoing prospective, double-blind placebo controlled study is being conducted by scientists at Washington University to determine if the rate of postcranial bone loss is related to the rate of alveolar bone loss and to determine the effect of ERT on bone-loss rates at these sites. Initial results indicate that alveolar bone loss is correlated with postcranial bone loss and that alveolar bone loss increases with years since menopause, cigarette smoking, and parity. Data is being obtained to determine whether HRT arrests or reduces the rate of alveolar bone loss, and thus can potentially help prevent or delay loss of teeth in elderly women.

National Institute of Dental and Craniofacial Research

Menopause-related projects

I. NIDCR Supported Projects - Directly Related to Menopause (Osteoporosis)

Contract #	Last Year Active	Institution	Title	Abstract
NO1 DE52605	2001	University of Alabama at Birmingham	Oral hard tissues status in relation to skeletal bone density measures & osteoporosis	The purpose of this program is to examine the relationship between oral bone density and systemic bone density in peri- and postmenopausal women, and to assess the severity of alveolar bone loss, residual ridge resorption, and tooth loss in patients with decreased skeletal bone density. Also under evaluation is whether hormone replacement therapy affects alveolar and residual bone loss. The collaborators will recruit 1,000 subjects from the observational study component of the parent trial that will include 60% minority subjects. The data obtained at baseline, three and six years, which includes systemic bone mass and comprehensive medical measurements and history, will be correlated with dental examinations and quantitative digital intraoral radiography.
5 R01 DE009861	2001	Washington University	Alveolar vs postcranial bone loss after menopause	Some postmenopausal women rapidly lose postcranial bone, and estrogen replacement therapy (ERT) can reduce this loss. This applicant is studying healthy postmenopausal women in a prospective, double-blind, placebo-controlled investigation to determine if the rate of postcranial bone loss is related to the rate of alveolar bone loss and to determine the effect of ERT on bone-loss rates at these sites. Initial results indicate that alveolar bone loss is correlated with postcranial bone loss and that alveolar bone loss increases with years since menopause, cigarette smoking and parity. To further understand the effect of hormonal replacement therapy as a preventive measure for alveolar and postcranial bone loss in postmenopausal women, the applicant is testing the hypothesis that HRT arrests or reduces the rate of postcranial bone deterioration after menopause and that it will similarly affect alveolar bone loss, and thus prevent or delay loss of teeth.

II. NIDCR Supported Projects - Hormones and Pain (Menopause relevant)

Grant #	Last Year Active	Organization	Project Title	Abstract
5 R01 DE012763	2001	New York State Psychiatric Institute	Pain and analgesic response-sex and hormone variations	The majority of studies involving experimentally-induced pain have shown that women are more sensitive to pain than men. However, many of the pain procedures that have found sex differences confound sensory (the ability to discriminate pain) and emotional (subjective reports of pain) variables by treating pain as a single dimension, when in fact pain varies along a range of dimensions. Further, while data suggest that sex differences in pain response may be related to circulating gonadal hormones, the definition and measurement of menstrual cycle phase has been inadequate. The purpose of the present application is to more fully investigate sex differences in response to painful stimuli, specifically focusing on 1) the influence of gonadal hormones on pain responsivity and 2) the analgesic response to mu (morphine) and kappa (butorphanol) opioid agonists.
5 R01 DE012470	2001	University of Washington	Menstrual cycle effects on TMD pain and other symptoms	Temporomandibular disorders (TMD's) are musculoskeletal pain conditions characterized by pain in the muscles of mastication and/or the temporomandibular joint. These pain problems are about twice as common in women as in men in the community, and prevalence peaks during the reproductive years. About 80 percent of patients treated in tertiary care settings are women. The investigators propose a 5-year program of clinical epidemiologic and experimental research to examine the possible interactive influences of hormonal status, other gender factors in pain sensitivity, the presence of non-TMD somatic symptoms and psychological distress on TMD pain in women.
5 R01 DE012757	2001	University of Maryland, Baltimore	Gonadal steroid hormonal regulation of persistent pain	This project is evaluating the effects of progesterone and progesterone in combination with estrogen on the hyperalgesia and hyperexcitability associated with a rat model of persistent pain and inflammation. The major hypothesis is that endogenous reproductive hormones can suppress persistent pain by their influence on a cascade of molecular, biochemical and physiological events at the spinal level involving inhibitory and excitatory amino acids and their receptors, and opioid peptides and their receptors. The principal investigator proposes to investigate the effects of these hormones on behavioral hyperalgesia, spinal cord neurons, modulation of GABA receptors, expression of opioid receptor and opioid peptides, and NMDA receptor function.

II. NIDCR Supported Projects - Hormones and Pain (Menopause relevant) continued…

5 RO3 DE013438	2001	University of Washington	Menstrual cycle and blood effects on acute pain	The study will assess blood pressure variability and variability in responses to ischemic pain at critical points (menses, ovulatory, mid-luteal and late luteal/premenstrual phases) across three consecutive ovulatory cycles in female TMD cases and appropriate controls, to ascertain the extent to which variability in blood pressures and pain may be attributable to female gender, hormonal status, and/or presence of clinical TMD pain. Thus, the proposed study will determine the discriminative ability of the tourniquet test for distinguishing female and male TMD patients from same-sex, pain free controls and evaluate the inter-relationships between menstrual cycle, blood pressure and pain.
3 R01 DE012725	2001	New York State Psychiatric Institute	Gender differences in pain sensation and pain report	Studies will be conducted at 5 precisely defined menstrual phases in normally cycling women, time-matched to men. Sensory Decision Theory (SDT) will be used to explore the hypothesis that women's more "sensitive" traditional thresholds are largely, but not entirely, due to a response bias (B) to report more pain, rather than to differences in discrimination sensitivity, P(A). Both SDT measures are expected to vary during the menstrual cycle. To test the hypothesis that women have a more sensitive secondary pain (C-fiber) system, responsiveness to brief stimuli will be obtained as parameters of heat (rise-time) and cold (adaptation level) are varied.
5 R01 DE011972	2001	University of Michigan at Ann Arbor	Neuroendocrinology of masticatory muscle disorders (MMDs)	This study will examine the comorbidity of MMD and disorders associated with hypothalamic-pituitary-adrenal (HPA) stress axis dysregulation including fibromyalgia and stress-related psychiatric disorders, including depression, and test the hypothesis that women with MMD have an underlying HPA axis abnormality similar to that which occurs in fibromyalgia, namely HPA axis hypofunction, which is the underlying pathophysiological basis of both disorders. HPA function will be studied in women with MMD, (with and without comorbid fibromyalgia and depression) compared to normal controls, in terms of circadian and pulsatile patterns of basal cortisol secretion, using an intensive 24-hour plasma cortisol sampling paradigm. Women will be studied during both follicular and luteal phases of the menstrual cycle to test the hypothesis that there will be menstrual cycle-phase related fluctuations in symptoms and HPA axis function.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

(NIAID)

National Institute of Allergy and Infectious Disease

The National Institute of Allergy and Infectious Diseases (NIAID) stands at the forefront of scientific research on a number of diseases that threaten the survival and quality of life of millions of people. NIAID conducted and sponsored research focuses on the diagnosis, treatment, and prevention of the full spectrum of infectious diseases as well as disorders of the immune response. The Institute maintains a strong commitment to basic, applied, and clinical investigations. Among the infectious diseases addressed by NIAID are the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS), other sexually transmitted diseases (STDs), and tuberculosis (TB). Immune mediated diseases that are addressed by NIAID include asthma and allergic diseases, autoimmune diseases, and transplantation. All of these diseases affect women as well as men and many women who have reached menopause or are post-menopausal.

Throughout the world, HIV is spread predominantly through sexual transmission. Therefore, the development of chemical and physical barriers that can be used intravaginally or intrarectally to inactivate HIV and other sexually transmitted diseases (STDs) is critically important for controlling HIV infection. Worldwide, women face the greatest risk of acquiring HIV due to substantial mucosal exposure to seminal fluids, high prevalence of non-consensual sex, sex without condom use, and hidden, high-risk behaviors of their partners. As a result of menopause, some women have low levels of the sex hormone, estrogen and are likely to be at higher risk of HIV infection. Despite the overwhelming risks presented to them, women have the fewest available means for protection against HIV and other STDs. An inexpensive, reliable, female-controlled method for preventing STDs is needed so that women can protect themselves. Ideally, chemical barriers, known as topical microbicides, should be invisible, non-irritating, and inexpensive. In addition, microbicides should be available in both spermicidal and non-spermicidal formulations to protect women who presently put themselves at risk of acquiring HIV and other STDs.

NIAID's research effort for the development of topical microbicides includes basic research, preclinical product development, and clinical evaluation. Population-based research is essential to evaluate the efficacy and effectiveness of intervention strategies, such as topical microbicides, which are designed to decrease or eliminate HIV transmission.

In addition to research on topical microbicides, NIAID conducts a variety of studies that indirectly affect menopausal women is listed below under programmatic accomplishments/developments.

SCIENCE ADVANCES:

BufferGel, a novel microbicide, shown to be safe and acceptable in multisite international Phase I trial. There is an urgent need for topically applied microbicides that are safe, acceptable and effective in preventing HIV transmission. BufferGel is a non-detergent-based microbicide that buffers vaginal pH, in the presence of semen, and thereby maintains the acidic environment of the vagina, which is hostile to HIV and other sexually transmitted disease (STD) pathogens. Results of a Phase I trial of low-risk women in the United States showed that BufferGel was non-toxic and well tolerated. An expanded Phase I trial was then conducted to examine the safety, acceptability and use of BufferGel in relevant international populations. HIV/STD-negative women in India, Thailand, Malawi and Zimbabwe participated in this trial in which BufferGel was applied twice a day for 14 days. Compliance and product use were high among all the sites and overall acceptability was high across sites, except in India. About half of the women in the study, including both sexually abstinent and sexually active women, developed at least one adverse event (AE) that **may** have been related to product use. Only 3% of the women experienced itching as a result of using the product. All AEs were mild or moderate and 93% resolved during or soon after the trial. No serious adverse events were reported and the trial raised no major concerns about safety.

Investigators: K. Mayer, K. Nelson Ref: Bentley M. et al: Abstract TuPpC1170 presented at the XIIIth International AIDS Conference in Durban, South Africa, 2000; Van de Bijgert J. et al: Abstract ThPeC5291 presented at the XIIIth International AIDS Conference in Durban, South Africa, 2000. Source: N01-AI-35176 Contact: Roberta Black (6-8199)

Prevention of vaginal transmission of simian immunodeficiency virus (SIV) by estrogen. As a result of menopause or treatment with the contraceptive, depo-medroxyprogesterone acetate (DMPA), some women have low levels of the sex hormone, estrogen and are likely to be at higher risk of HIV infection. Among its many functions, estrogen promotes thickening of the vaginal mucosa, which represents a major physical barrier to infection. To understand the individual roles of estrogen and progesterone on the vaginal epithelia and vaginal transmission, female macaques were first ovariectomized to eliminate endogenous hormone production and then treated with either progesterone or estrogen. Following intravaginal inoculation with SIV, untreated control or progesterone-treated macaques (11/12) became infected while none of the 6 estrogen-treated macaques were infected. To confirm that the infection was blocked at the vaginal epithelium, subepithelial inoculation of the estrogen-treated macaques was performed. Infection resulted when the vaginal epithelium was bypassed. This study suggests that women with low estrogen levels may be at increased risk of HIV infection because the vaginal microenvironment is more susceptible to infection.

Investigator: P. Marx Ref: Smith SM. et al: JID (2000) In press. Source: R01-AI-41952 Contact : Opendra Sharma

PROGRAMMATIC ACCOMPLISHMENTS/DEVELOPMENTS

- A Request for Proposals (RFP-01-017), **"Primate Models to Evaluate HIV Prevention & Therapeutic Strategies"**, was issued to maintain the Division of AIDS' capability to evaluate microbicides and potential therapies. This resource will be used for: 1) studies of new microbicide or therapeutic approaches where "proof of concept" in a primate model would provide critical information to advance development; 2) studies that cannot be addressed in other animal models of HIV infection for lack of appropriate viral or cellular target; 3) candidates/strategies in an advanced stage of development that require optimization; 4) confirmatory studies of candidates/strategies that have proven promising in other animal models of HIV infection.

- A second RFP (RFP-01-04), **"Simian Vaccine Evaluation Units,"** the primary purpose of which is to provide non-human primates for immunization with candidate SIV or HIV vaccines, has additional capacity for microbicide testing to complement RFP-01-017. New awards will be made during the FY2001.

- PAR-00-098, **"Novel HIV Therapies: Integrated Preclinical/Clinical Program"**, was released to continue to stimulate iterative preclinical and clinical research for novel therapeutic and microbicide strategies against HIV infection. The overall goal of the IPCP is to establish proof-of-principle of new and pioneering therapeutic or microbicide modalities in a small number of patients, and then segue these studies to large clinical trials under the ACTG or HPTN network. This PA is a re-release of the original IPCP PA (PAR-97-080), released July 1997 but unlike the original PA, groups responding to the PA must have formal interaction with the private sector to expedite the development of promising therapeutics or microbicides.

    - **AACTG 5119**: Pharmacokenetic interaction between selected Protease Inhibitors, Efavirenz and hormone replacement therapy in HIV+ Postmenopausal women and some protocols aimed specifically at women (to possibly include menopausal women. (in development)

    - **A5137**: Randomized Phase I/II Pilot Study of Intermittent Withdrawal of ARV Treatment as Immunication Strategy and Double-Blinded Immuniation with ALVAC-HIV v CP1452 in Subjects with Persistent CD4+Cell Counts>500 Cells/MM3 & Plasma RANA <50 copies/MM3.

    - **ACTG 317**: The Effect of Oral and Injectable Contraceptives (Norethindrone/Ethinyl Estradiol, Medoxyprogesterone Acetate) and Gender on Plasma and intracellular Zidovudine Pharmacokinetics.

The following contracts were awarded in response to Request for Proposals (RFPs) issued last year. These resources support discovery and development of novel HIV therapeutics and microbicides and are accessible by the scientific community.

- Contract N01-AI-05400, entitled **"Analytical Chemistry Evaluation of Therapeutic Agents"**, to support the development and utilization of analytical assays for evaluating therapeutic agents. The contract has been awarded to Research Triangle Institute for a period of 7 years beginning February 2000.

- Contract N01-AI-05402, entitled **"Resynthesis of Therapeutic Agents for Treatment of Infectious Diseases"**, for synthesis of chemicals in compliance with FDA Good Manufacturing Practice (GMP) regulations and in quantities needed for testing in either in vitro screens, animals, or early Phase I clinical studies. The contract has been awarded to Starks Associates, Inc. for a period of 7 years beginning February 2000.

- Contract N01-AI 05414, entitled **"Development and Manufacture of Dosage Forms for Compounds with Potential for Treatment of Infectious Diseases"**, for drug formulation development and clinical dosage form manufacturing. The contract has been awarded to SRI International for a period of 5 years beginning May 2000.

- Contract N01-AI 05417, entitled **"Safety Evaluation of Anti-Infective Therapies"**, for toxicology and pharmacokinetic testing of new anti-infective therapies and microbicides. The contract has been awarded to SRI International for a period of 7 years beginning July 2000.

- Contract N01-AI-05415, entitled **"Specialized in vitro Virological Evaluations of Strategies to Combat HIV/AIDS"**, to support the development and utilization of assays for evaluating topical microbicides and therapeutic agents. The contract has been awarded to Southern Research Institute, for a period of 7 years beginning July 2000.

- **"Confirmatory In vitro Virological Evaluations of Strategies to Combat HIV/AIDS"** to support the development and utilization of in vitro virologic assays for evaluating therapeutic agents. The proposed award date for the contract is September 2000.

In vitro screening of potential topical microbicides is provided by DAIDS contract resources. Primary screening of candidate microbicides is completed in CD4-dependent and CD4-independent assays in the presence and absence of mucin, to mimic the vaginal environment. Viral binding and fusion assays are utilized as secondary screens to further elucidate compound mechanism of action. Finally, compounds found to be active in the primary screens are evaluated for potential toxicity against two strains of Lactobacillus that colonize the healthy human vagina and represent a potential nonspecific protective barrier against sexually transmitted infections. Approximately 1700 compounds have now been examined in one or more of these assays. The colorless, or lightly colored

compounds with a high therapeutic index (>10) are undergoing additional evaluation to assess their potential to be developed as topical microbicides.

The HIV Prevention Trials Network was established in July 2000. The network encompasses an operations center, central laboratory and statistical and data management and 26 domestic and international units. Topical microbicides will be a major area of emphasis for the network.

A randomized, placebo-controlled Phase I/II trial to assess the safety, acceptability and preliminary effectiveness of a lambda-carageenan (PC515), a non-contraceptive sulfated polysaccharide microbicide, was initiated at several sites in South Africa. Dr. Charlotte Ellertson of the Population Council is the Principal Investigator of this trial, supported by R01 AI45468.

HIVNET 016, a Phase III study to assess the effectiveness of 100mg intravaginal N-9 gel (Conceptrol®) in preventing male to female sexual transmission of HIV was placed on hold. Recently released preliminary analyses of a Phase III microbicide trial of Advantage-S® (containing 52.5 mg N-9) gel have indicated that N-9 may increase the rate of sexual transmission of HIV.

FUTURE PLANS

An RFA will be issued for the "Management of Information Resources on Therapeutic Agents for HIV and Opportunistic Infections." This will provide a computerized chemical database tool for the rational selection and discovery of potential therapies for HIV and its complications, utilized by both the scientific community and NIAID.